IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JOHNS HOPKINS UNIVERSITY,	:	
	:	
Plaintiff,	:	
	:	
v.	:	C.A. No. 13-1853-LPS
	:	
454 LIFE SCIENCES CORPORATION,	:	
	:	
Defendant.	:	

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MEMORANDUM OPINION

January 26, 2017
Wilmington, Delaware

STARK, U.S. District Judge:

On November 6, 2013, Johns Hopkins University ("JHU" or "Plaintiff") filed this action pursuant to 35 U.S.C. § 146, seeking review of the Decision and Final Judgment of the Board of Patent Appeals and Interferences ("the Board") in Interference No. 105,857 ("the Interference"). (*See* D.I. 1 at 1, 8; Statement of Admitted Facts ("SAF") D.I. 102-1 ¶ 1) The interfering applications are JHU's U.S. Patent Application No. 12/361,690 (D.I. 39 Ex. 1) (JHU's "'690 application") and U.S. Patent Application No. 13/33,240 (D.I. 39 Ex. 5) (454's "'240 application"), which was filed by Defendant 454 Life Sciences Corporation ("454" or "Defendant"). The Interference involves a single count ("Count"),[1] with the interfering subject matter represented by claim 1 of JHU's '690 application and claim 52 of 454's '240 application. (*See* D.I. 44 at 1; D.I. 45 at 1)

Claim 1 of JHU's '690 application recites the following four-step method:

> A method for analyzing nucleic acid sequences comprising:
>
> > (a) generating a plurality of molecules of a fragment of deoxyribonucleic acid;
> >
> > (b) delivering the plurality of molecules of the fragment of deoxyribonucleic acid into aqueous microreactors in a water-in-oil emulsion such that a plurality of aqueous microreactors comprise a single molecule of the fragment of deoxyribonucleic acid, a single bead capable of hybridizing the fragment of deoxyribonucleic acid, and reagents necessary to perform deoxyribonucleic acid amplification;

[1]In an interference, "[t]he applicant must identify at least one patentable claim from every application or patent that interferes for each count. A count is just a description of the interfering subject matter, which the Board of Patent Appeals and Interferences uses to determine what evidence may be used to prove priority under 35 U.S.C. § 102(g)(1)." Manual of Patent Examining Procedure ("MPEP") § 2304.02(b).

> (c) amplifying the fragment of deoxyribonucleic acid in the microreactors to form amplified copies of said fragment of deoxyribonucleic acid bound to beads in the microreactors; [and]
>
> (d) determining presence of amplified copies of said fragment of deoxyribonucleic acid bound to a bead.

(D.I. 44 at 2-3)[2]

The Court held a claim construction hearing on June 9, 2015 and issued a memorandum opinion on claim construction on August 24, 2015. (D.I. 56) Thereafter, the parties filed summary judgment motions. On May 2, 2016, the Court denied all summary judgment motions, with the exception of JHU's motion for partial summary judgment that JHU's priority date with respect to the Count is no later than June 5, 2003, which the Court granted. (*See generally* D.I. 97, 98)

The Court held a bench trial on all remaining issues in June 2016. (*See* Transcript, D.I. 112, 113, 114 ("Tr.")) The parties later submitted post-trial briefing (D.I. 108, 110, 115, 118) and proposed findings of fact (D.I. 109, 111, 116, 117).

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the Court concludes that: (1) JHU has failed to prove that it is entitled to priority of invention, and (2) JHU has failed to prove that 454's '240 application is invalid.

The Court's findings of fact and conclusions of law are set forth in detail below.

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[2]All pending claims of the '690 application (claims 1, 2, 5-17) and the '240 application (claims 52-66) correspond to the single Count in the Interference.

FINDINGS OF FACT

This section contains the Court's findings of fact for issues raised by the parties during trial. Certain findings of fact are also provided in connection with the Court's conclusions of law.

A. Patent Applications at Issue

1. Plaintiff JHU's '690 application, entitled "Method and Compositions for Detection and Enumeration of Genetic Variations," was filed on January 29, 2009. (D.I. 22-1 Document 1) The named inventors are Devin Dressman, Hai Yan, Kenneth W. Kinzler, and Bert Vogelstein. (*Id.*)

2. Defendant 454's '240 application, entitled "Bead Emulsion Nucleic Acid Amplification," was filed on February 23, 2011. (ATX 1001)[3] The named inventors are Gary Sarkis, Jan Berka, John Leamon, Kenton Lohman, Maithreyan Srinivasan, Yi-Ju Chen, Vinod Makhijani, Jonathan Rothberg, Steve Lefkowitz, and Michael Weiner. (*Id.*) The '240 application issued as U.S. Patent No. 8,748,102 ("'102 patent") on June 10, 2014. (DTX 12)[4]

3. The '240 application is a continuation of U.S. Patent Application No. 11/982,095, filed on October 31, 2007 (ATX 1005), which is a continuation of U.S. Patent Application No. 10/767,899 ("'899 application"), filed on January 28, 2004 (ATX 1007). The '899 application claims benefit to a number of provisional applications, including U.S. Provisional Patent

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[3]The Court admitted exhibits from the Interference into evidence (ATX). (*See* D.I. 21-32) The parties submitted a list correlating exhibit numbers to document descriptions in their joint proposed pretrial order. (D.I. 102 Ex. 8A1)

[4]Exhibits submitted by Plaintiff (PTX) and Defendant (DTX) that are cited herein were admitted into evidence.

Application No. 60/476,592, filed June 6, 2003 ("'592 provisional" or "'592 application") (ATX 1013), and U.S. Provisional Patent Application No. 60/465,071, filed April 23, 2003 ("'071 provisional" or "'071 application") (ATX 1015).

4. The contents of the '071 and '592 provisional applications are incorporated by reference in their entirety into the '240 application. ('240 application at 1:3-6)

5. The '240 application also incorporates by reference co-pending U.S. Patent Application No. 10/767,779 ("'779 application"), which issued as U.S. Patent No. 7,323,305 ("'305 patent") on January 29, 2008. (ATX 1001; DTX 12; DTX 13) The '305 patent contains the entire disclosure of the '592 provisional. (*Id.*)

B. Procedural History in the Patent Office

6. The Board initially accorded JHU a priority date of July 5, 2003 and 454 a priority date of June 6, 2003 (the filing date of the '592 provisional), making JHU the junior party and 454 the senior party in the Interference. (*See* ATX 236 at 3:16-26)

7. In the Interference, JHU filed a motion attacking 454's claim to the '592 provisional's filing date. (D.I. 23-4 at 7:6-13) The Board denied JHU's motion, ruling that JHU had failed to show that the '592 provisional did not disclose a reduction to practice within the scope of the Count. (*Id.*)

8. In the Interference, 454 filed a motion to obtain the benefit of the '071 application. (ATX 236 at 8:11-16) The Board denied 454's motion, finding that 454 had failed to establish adequate written description support in the '071 application. (*Id.* at 15:24-26) Specifically, the Board found that "454 ha[d] not established (e.g., by citing to data or expert testimony)" that use of restriction enzymes recited in the '071 application "would generate two or

more molecules of a specific DNA fragment, or more specifically, that an ordinary artisan would understand that to be the case," as required to practice step (a) of the Count. (*Id.* at 14:13-18)

9. During the priority stage, JHU submitted evidence of priority from the January to May 2003 time frame. (ATX 370 at 5 n.1) However, the Board found that the "evidence cited by JHU does not sufficiently establish that JHU conceived of the subject matter of Count 1 in the January to May 2003 time frame." (*Id.*) Specifically, the Board found that the evidence "[did] not adequately show JHU conceived of elements (a) and (b)" of the Count during that time frame. (*Id.*) The Board also found that "JHU offer[ed] insufficient non-inventor evidence (testimony or otherwise) to corroborate conception by the JHU inventors at that time." (*Id.*) As a result, the Board accorded JHU a June 5, 2003 conception date. (*Id.* at 7:16-22) The Board found that JHU reduced the invention to practice one month later, on July 5, 2003. (*Id.*)

10. With respect to 454, the Board concluded that a preponderance of the evidence showed and corroborated the fact that the 454 inventors conceived of all elements of the Count before June 2003. (ATX 370 at 17:1-23:9) In particular, the Board found the combination of page 16 of the notebook of Dr. Jan Berka (one of the 454 inventors) (ATX 1094), evidence regarding experiments conducted between August and December 2002, evidence of experiments conducted in January and February 2003, a "Best Practices" document from February 2003 (ATX 1102; ATX 1103), and an invention disclosure form (ATX 1106 at 107-12), taken as a whole, established that the 454 inventors conceived the subject matter of the Count before JHU's earliest accorded date. (ATX 370 at 21:7-23:2)

11. The Board held that "as long as the inventors conceived of performing [step] (a), i.e., generating a plurality of molecules of a particular fragment of DNA, along with [steps] (b)

through (d), it [did] not matter whether the inventors failed 'to appreciate the value of step (a)' beyond its use to generate a control used in the method [as alleged by JHU]." (ATX 370 at 18:20-19:3) The Board further held that the "evidence establishe[d] that the inventors appreciated that [step] (a) took place, regardless of its 'value' in relation to benefits of the protocol in amplifying genomic template DNA." (*Id.* at 19:3-5)

12. The Board awarded priority of invention to 454, finding that 454 conceived of the invention of the Count before JHU's conception and was also first to reduce the invention to practice. (ATX 370 at 23:8-9)

C. The Court's Claim Constructions[5]

13. The Court construed the term "generating a plurality of molecules of a fragment of deoxyribonucleic acid" in step (a) to mean "generating two or more of the same DNA fragment, not merely generating a plurality of DNA fragments overall." (D.I. 57 at 2) The Court's construction of step (a) does not require any particular method of generating two or more copies of the same DNA fragment. (Levy Tr. at 367:9-19)[6] However, the fragment formed in step (a) is a sequence that is ultimately amplified in the emulsion and sequenced. (*Id.* at 505:8-17)

14. The Court determined that the following term required no further construction:

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[5]In this Opinion, the Court applies the broadest reasonable interpretation of the various terms of representative claim 1 of the '690 application in light of the "originating disclosure." *See ULF Bamberg v. Dalvey*, 815 F.3d 793, 796 (Fed. Cir. 2016). The Court previously determined that the "originating disclosure" in this case is JHU's '690 application and its prosecution history, which includes references to some of 454's patent applications. (*See* D.I. 56 at 8)

[6]The Court refers to testimony given at trial by a particular witness in the following format: "([Witness Last Name] Tr. at [page:line(s)])."

"delivering the plurality of molecules of the fragment of deoxyribonucleic acid into aqueous microreactors in a water-in-oil emulsion such that a plurality of aqueous microreactors comprise a single molecule of the fragment of deoxyribonucleic acid, a single bead capable of hybridizing to the fragment of deoxyribonucleic acid, and regents necessary to perform deoxyribonucleic acid amplification." (D.I. 57 at 2) There is no significant distinction between delivering to a microreactor double-stranded DNA separately from a bead versus delivering single-stranded DNA pre-hybridized to a bead. (Levy Tr. at 405:8-24, 470:14-19; *see also* Tyagi Tr. at 116:13-15)

15. The Court construed the terms "deoxyribonucleic acid" and "DNA" to mean "a nucleic acid molecule comprising deoxyribonucleotides." (D.I. 57 at 2) Single-stranded DNA is a nucleic acid molecule comprising deoxyribonucleotides. (Levy Tr. at 404:3-9)

16. The Court construed the term "a single bead capable of hybridizing to the fragment" to mean "a single bead capable of binding to the fragment of deoxyribonucleic acid." (D.I. 57 at 2) The Court's construction of "a single bead capable of hybridizing to the fragment" only requires that a bead be capable of hybridizing to the DNA fragment. (Levy Tr. at 390:16-391:14) A bead that has bound to the fragment is capable of binding, and a bead that has not bound to a fragment may also be capable of binding. (*Id.*)

17. The Count may be satisfied even if the fragment from step (a) is pre-hybridized to a bead before delivery to a microreactor. (*Id.* at 505:18-506:1) The sequence of the fragment formed in step (a) remains intact regardless of whether it is hybridized to the bead. (*Id.* at 391:24-393:14) Moreover, when the fragment of DNA hybridizes to the bead, it does not create a new molecule. (*Id.*) The DNA fragment and the bead retain their individual identity, even

while hybridized. (*Id.* at 393:10-14, 459:19-460:4)

18. Hybridization of the DNA fragment to the bead is through hydrogen bonding, which is a non-covalent, electrostatic interaction. (*Id.* at 392:16-393:9) Hydrogen bonding can be thought of like a sock sticking to a sweater when it is pulled out of a dryer. (*Id.*) Just because a sock is stuck to a sweater does not mean a new entity has formed. (*Id.*) Similarly, just because a DNA fragment has hybridized to a bead does not mean a new molecule has formed. (*Id.*)

D. Person of Ordinary Skill in the Art

19. One of ordinary skill in the art at the pertinent time would have had around four years of research experience, a Master's degree or Ph.D. in molecular biology or other related fields such as genetics or biochemistry, and would have been familiar with polymerase chain reaction ("PCR"). (Tyagi Tr. at 45:25-46:7; Levy Tr. at 353:7-354:4) A person of ordinary skill in the art would have been aware of emulsion PCR as a general concept. (Levy Tr. at 353:25-354:4 (stating that at time of invention "there were a couple of very high profile papers that describe[d] using emulsions to either do PCR, in the case of the Hollinger paper, or to use emulsions to encapsulate other things"); ATX 1099; ATX 1097 at 4)

E. JHU's Witnesses

20. JHU called just a single witness to testify live at trial. Dr. Sanjay Tyagi obtained a B.S. from the University of Rajasthan in India, two M.S. degrees in biology from the Jawaharlal Nehru University in New Delhi, and a Ph.D. from the University of Maryland. (Tyagi Tr. at 42:16-21; PTX 001)

21. Since 1987, Dr. Tyagi has worked at the Public Health Associate Institute, which currently is a part of Rutgers University, initially as Associate Professor and currently as a full

Professor. (*Id.* at 42:24-43:2) Dr. Tyagi has 29 years of postdoctoral experience in the field of nucleic acids, molecular biology, and cell biology research. (*Id.* at 43:5-44:7)

22. JHU called several other witnesses to testify by reading some or all of the declaration(s) these witnesses submitted as part of the Interference proceedings. (*See* Tr. at 164:21-175:3; ATX 2024, 2034, 2051, 2079, 2080)

23. JHU presented testimony from six witnesses by declaration:

a. Dr. Bert Vogelstein is a professor of oncology at Johns Hopkins University School of Medicine, Baltimore, MD, and a Howard Hughes Medical Institute investigator. (ATX 2034 ¶ 2) Dr. Vogelstein supervised the work of Dr. Devin Dressman as a post-doctoral fellow in his and Dr. Kenneth Kinzler's laboratory beginning at the end of January 2003 and continuing beyond July 5, 2003. (*Id.* ¶ 3)

b. Dr. Devin Dressman currently works in research and development for Life Technologies Corporation in Beverly, MA. (ATX 2051 ¶ 2) He is in the "Ion Torrent" division at Life Technologies, which deals with a sequencing system that utilizes bead emulsion amplification for sequencing sample preparation. (*Id.*) Dr. Dressman worked as a post-doctoral fellow in the laboratory of Drs. Kenneth Kinzler and Bert Vogelstein at Johns Hopkins University beginning at the end of January 2003 and continuing beyond July 5, 2003. (*Id.* ¶ 3)

c. Dr. Hai Yan worked with Dr. Dressman between January 2003 and July 5, 2003 on bead emulsion amplification projects. (*Id.*)

d. Dr. Kenneth Kinzler ran a laboratory with Dr. Vogelstein at Johns Hopkins University, as discussed above. (ATX 2034 ¶ 3)

e. Ms. Leslie Meszler held the position of Core Manager at the Cell Imaging

Core at Johns Hopkins University in 2003. (ATX 2029 ¶ 1) She was responsible for managing the day-to-day operations of the Cell Imaging Core during 2003. (*Id.*) One of her responsibilities included tracking scientists' use of a flow cytometer. (*Id.* ¶¶ 3-5) She testified (by declaration) that the flow cytometer was used by Dr. Dressman during the week of April 20, 2003. (*Id.* ¶ 6)

f. Mr. Jason Briody is an Associate at Jones Dykstra & Associates, a specialized services company that provides computer forensics, electronic data discovery, litigation support, training, and computer security services for commercial and governmental clients. (ATX 2081 at 6) Mr. Briody is primarily responsible for planning and technically executing electronic discovery projects and performing computer forensic analysis. (*Id.*) Mr. Briody analyzed files given to him by Johns Hopkins University for authentication purposes related to this litigation. (*Id.* at 4-5)

F. 454's Witnesses

24. Dr. Matthew Levy testified live at trial. The Court found him to be credible and persuasive on every material point.

25. Dr. Levy earned a B.S. in biochemistry and a M.S. in chemistry, both from the University of California San Diego, and a Ph.D. in molecular biology from the University of Texas. (DTX 32; Levy Tr. at 347:18-348:7) Dr. Levy is an Associate Professor of biochemistry at the Albert Einstein College of Medicine. (DTX 32; Levy Tr. at 348:10-17) Dr. Levy teaches a variety of classes, including biochemistry, immunology, and chemical biology. (Levy Tr. at 348:19-21) A major focus of his research is developing nucleic acid-based therapeutics and diagnostics. (*Id.* at 349:3-7) He is familiar with genomic DNA isolation, DNA sequencing, and emulsion PCR. (*Id.* at 349:14-350:1) Dr. Levy has personally conducted emulsion PCR and has

experience making emulsions for emulsion PCR. (*Id.* at 349:18-21)

26. Dr. Gary J. Sarkis is one of the 454 inventors. Dr. Sarkis received a B.S. in microbiology and an M.S. in biochemistry and molecular genetics, both from the University of Pittsburgh. He also received a Ph.D. in molecular, cellular, and developmental biology from the University of Pittsburgh in 1997. He was a postdoctoral research fellow at Yale University from 1997 to 2002 and was employed at 454 as a research scientist, section leader (sample preparation), training manager, and customer support manager from 2002 to 2006. (Sarkis Tr. at 177:11-15, 178:5-179:4) He testified live at trial.

27. Janna Lanza Thompson received a B.S. in biology from the University of Vermont and a M.S. in cell and molecular biology from Central Connecticut State University. She was employed at 454 as a research associate from 2001 to 2006. (Lanza Tr. at 278:3-279:2) She testified live at trial.

28. Dr. Alex de Winter received a B.A. in chemistry from Amherst College and a Ph.D. in chemistry from Stanford University. He was employed at 454 as a research scientist from 2001 to 2004. (de Winter Tr. at 322:22-324:9) He testified live at trial.

29. Dr. Jan Berka is one of the 454 inventors. He received a B.S. and M.S. in molecular biology and genetics and a Ph.D. in molecular biology and genetics, all from Masaryk University, Brno, Czech Republic. He was a postdoctoral research fellow at the Barnett Institute at Northeastern University in Boston from 1992 to 1996. Dr. Berka was employed at 454 as a senior scientist and director from 2000-2006. (ATX 1113 ¶¶ 2-3) Dr. Berka testified by declaration.

30. Dr. Maithreyan Srinivasan is one of the 454 inventors. Dr. Srinivasan has a Ph.D.

in biochemistry. He was employed at 454 as a project leader in the Protein Sciences group from 2000-2007. (ATX 1116 ¶¶ 2-3) He testified by declaration.

31. Mr. Keith McDade received a B.S. in molecular biology from the University of Connecticut and a M.S. in computer science from the University of New Haven. He was employed at 454 as a research associate from 2000 to 2006. (ATX 1124 ¶¶ 2-3) He testified by declaration.

32. Dr. John Leamon is one of the 454 inventors. Dr. Leamon received a B.A. in zoology and a Ph.D. in physiology from the University of Connecticut. He was a postdoctoral research fellow at the Yale School of Medicine from 1999-2001. Dr. Leamon was employed at 454 in various positions ranging from research scientist to group leader from 2001-2007. (ATX 1114 ¶¶ 2-3) He testified by declaration.

33. Dr. Louis Ferland received a B.S. in biochemistry from Université Laval and a Ph.D. in experimental medicine from McGill University. He was a postdoctoral research fellow at the Salk Institute, Regulatory Biology Department from 1986-1989; and at the Institut Pasteur, Departement de Genetique Moleculaire du Developpement from 1989-1991. He was employed at 454 in various positions ranging from technical writer to manager of documentation from 2001-2012. (ATX 1118 ¶¶ 2-3) He testified by declaration.

34. Mr. William Altman received a B.S. in biology from Guilford College. He was employed at 454 from 2001 to 2013, holding several positions ranging from research assistant to senior customer support specialist. (ATX 1120 ¶¶ 2-3) He testified by declaration.

G. 454's Conception of the Invention by December 2002

35. Dr. Sarkis testified at trial, and previously submitted a declaration to the Board,

indicating that he recalls discussing the idea for a method for analyzing nucleic acid sequences using bead PCR emulsion amplification with Dr. Berka – which is reflected in Dr. Berka's laboratory notebook dated June 7, 2002. (Sarkis Tr. at 180:8-183:5; ATX 1115 ¶ 16; ATX 1094 at 16; ATX 1113 ¶ 18)

36. On June 7, 2002, Dr. Berka recorded in his lab notebook the notes of a conversation with Dr. Sarkis about the idea of PCR in water droplets in oil (water-in-oil emulsion) as individual microreactors that would contain a single effective copy of a sequence of DNA, a capture bead, and enough PCR reaction solution to produce amplified amounts of individual DNA fragments for massively parallel sequencing. (Sarkis Tr. at 180:8-183:5; ATX 1115 ¶ 17; ATX 1094 at 16; ATX 1113 ¶ 18)

37. That same page of Dr. Berka's notebook (page 16) also contains a drawing that depicts the concept of a PCR reaction occurring from a single bead and a single starting DNA fragment within the individual microreactors. (Sarkis Tr. at 182:7-23; ATX 1115 ¶¶ 17-20; ATX 1094 at 16; ATX 1113 ¶ 19) The drawing also shows the single-stranded DNA fragment attached to a primer on the capture bead and the resulting double-stranded DNA that would be present after the amplification process had begun. (ATX 1094 at 16) To the right of the drawing of the microreactor, Dr. Berka noted that "isolated bead bound primer extension" would occur "inside of the individual bead reactors." (Sarkis Tr. at 184:4-13; ATX 1115 ¶ 19; ATX 1094 at 16; ATX 1113 ¶ 20)

38. Dr. Maithreyan Srinivasan testified by declaration that he recalled discussing the idea for a method of analyzing nucleic acid sequences using bead emulsion amplification with Dr. Berka. (Srinivasan Tr. at 267:25-268:13; ATX 1116 ¶¶ 9-15) This idea, also recorded on

page 16 of Dr. Berka's notebook (ATX 1094), was contemporaneously witnessed and signed by Dr. Srinivasan on the same day it was written down by Dr. Berka: June 7, 2002. (*Id.*)

39. Dr. Leamon testified by declaration about experiments he performed in August 2002 to improve the stabilization of emulsions for bead emulsion PCR. Although Dr. Leamon was able to successfully form the emulsions, after a number of cycles the emulsions were breaking down or "crashing." (Leamon Tr. at 307:2-308:24; ATX 1096 at 110-12, 123; ATX 1114 ¶¶ 21-24)

40. On December 11, 2002, Dr. Leamon proposed the use of restriction endonuclease enzymes, known as "4-cutters," instead of DNase I, to digest DNA fragments. (Leamon Tr. at 308:25-309:17; ATX 1097 at 1; ATX 1114 ¶¶ 25-26) The '592 provisional specifically discloses using Sau31, MspI, and TaqI, which are 4-cutters. (Levy Tr. at 368:24-369:10; ATX 1013 at 11:24-26) Dr. Leamon recognized using 4-cutters would make DNA template with at least two copies of a fragment of DNA. (ATX 1114 ¶ 25) Dr. Leamon suggested using as many 4-cutters as prudent, perhaps 4 or 5, ligating adaptors onto each pool, and then hybridizing the DNA template onto the beads. (*Id.*)

41. On December 19, 2002, Drs. Leamon, Sarkis, and Berka attended a lecture at Yale University given by Jennifer Ong. (Sarkis Tr. at 186:18-187:22; ATX 1105 at 93; Leamon Tr. at 309:18-25; ATX 1095 at 69; ATX 1114 ¶ 27; Berka Tr. at 303:1-4; ATX 1113 ¶ 23) Dr. Ong is one of the co-authors of a well-known journal article entitled, "Directed evolution of polymerase function by compartmentalized self-replication," attributed to Ghadessy et al., and published in the journal of *Proceedings of the National Academy of Sciences* ("PNAS") on April 10, 2001 ("Ghadessy"). (ATX 1099; Sarkis Tr. at 187:23-188:13; DTX 33) Also on December 19, 2002,

Dr. Sarkis sequenced test fragments that 454 used as controls and obtained good sequencing results. (Sarkis Tr. at 192:19-193:2; ATX 1105 at 94)

42. Drs. Sarkis, Leamon, and Berka referenced the seminar given at Yale by Dr. Ong in their notebooks. (Sarkis Tr. at 186:18-187:22; ATX 1105 at 93; Berka Tr. at 303:1-4; ATX 1095 at 69; ATX 1113 ¶ 23; Leamon Tr. at 309:18-310:8; ATX 1114 ¶¶ 27-28) Dr. Leamon included an excerpt of the Ghadessy paper in his lab notebook and noted his belief that the emulsion information discussed by Dr. Ong could be used for emulsion PCR using a sepharose bead. (Sarkis Tr. at 188:3-190:1; Leamon Tr. at 309:18-310:8; ATX 1097 at 2-3; ATX 1114 ¶¶ 27-28) Dr. Leamon also noted that "Andrew Griffith's group has used emulsion based bead PCR bead capture for translation studies which suggests that the beads maintain their discrete micelle identity," and included an excerpt from an article by Armin Sepp, Dan Tawfik, and Andrew Griffiths ("Sepp"), regarding formation of emulsions, on the next page of his notebook on December 19, 2002. (ATX 1097 at 3-4) The Sepp article is entitled "Microbead display by in vitro compartmentalization selection for binding using flow cytometry," and was published in *Federation of European Biochemical Societies Letters* ("FEBS") in November 2002. (ATX 1100)

43. On December 20, 2002, the day after attending the lecture at Yale and reviewing the Ghadessy and Sepp references, Dr. Leamon performed an experiment and successfully prepared beads in a water-in-oil emulsion. (Sarkis Tr. at 190:2-16; ATX 1097 at 5-6; Leamon Tr. at 310:9-21; ATX 1114 ¶ 29; Levy Tr. at 446:24-447:17) Dr. Leamon included pictures in his notebook that demonstrate that some of the micelles were suitably-sized for the sepharose beads. (ATX 1114 ¶ 29)

44. Also on December 20, 2002, again the day after attending the lecture at Yale, Dr. Sarkis performed an emulsion PCR experiment with PCR-generated test fragments TF1, TF2, TF3, TF4, TF5, TF6, F6, and N7, and successfully amplified the test fragments. (Sarkis Tr. at 193:22-195:7; ATX 1105 at 95-96; Levy Tr. at 446:24-447:17) Dr. Sarkis's December 20, 2002 experiment evidenced conception of the invention of the Count, as further explained below.

45. Dr. Sarkis testified that the test fragments used by 454 originally came from Curagen Corporation, a sister company to 454. (Sarkis Tr. at 193:3-21) The fragments were labeled by the well number that they came from on the microtiter plates, and 454 knew the sequence of all of these test fragments. (*Id.*) The sequence of the F6 test fragment is recorded in Dr. Sarkis's lab notebook many times and was used for comparison each time the test fragment was sequenced in a reaction. (*Id.*)

46. The F6 test fragment was PCR amplified by Mr. Altman, a 454 research assistant, who testified by declaration about making the F6 test fragments. (Altman Tr. at 271:25-273:20; ATX 1120 ¶¶ 6-10; ATX 1108; ATX 1109) As recorded in his notebook, Mr. Altman successfully sequenced the F6 test fragments on July 22, 2002. (*Id.*; ATX 1109 at 13)

47. Ms. Lanza (now Ms. Thompson) testified that she recorded the sequence of the F6 test fragment, which was a PCR-generated fragment commonly used at 454, in her notebook on January 23, 2003. (Lanza Tr. at 280:1-20; ATX 1132 at 134; ATX 1126 ¶ 11) The sequence of F6 is identified on page 134 of her notebook, i.e., ATX 1132 at 134.

48. Dr. de Winter testified that all of the test fragments that were used as controls by the 454 scientists were PCR-generated fragments. (de Winter Tr. at 331:16-18) JHU's expert, Dr. Tyagi, testified that the test fragments, e.g., F6, would satisfy step (a) of the Count if they

were generated by PCR. (Tyagi Tr. at 90:5-19)

49. Dr. de Winter testified that he prepared adenovirus DNA libraries for use in the emulsion PCR project and testified about the process or standard operating procedure that he used to prepare the libraries. (de Winter Tr. at 324:6-9, 326:2-327:23, 330:17-331:4; ATX 1122 at 51-52, 65, 69, 71-72, 75-76, 78; ATX 1123 ¶¶ 10-11) The typical process for preparing the library would be to fragment the adenovirus, polish the ends of the fragments with polymerases or dNTPs, ligate adaptors to the ends of the polished fragments, purify the ligation products, capture on streptavidin-coated beads, and then elute the single-stranded DNA fragments. (ATX 1123 ¶ 10)

50. Dr. de Winter included in his notebook a detailed sample preparation protocol that he used for preparing adenovirus template libraries for emulsion PCR. (de Winter Tr. at 327:1-23, 330:1-11; ATX 1122 at 60) For this particular protocol, he usually used DNase I to fragment the adenovirus. (de Winter Tr. at 329:2-15, 330:5-16; ATX 1122 at 59)

51. Dr. de Winter testified that there are a number of ways to fragment DNA, including using restriction enzymes that recognize particular 4-base sequences. (de Winter Tr. at 331:24-332:6)

52. Restriction enzyme digestion can be used to generate overlapping genomic sequences for sequencing because they will each cut at a different site. (Tyagi Tr. at 125:15-19; Levy Tr. at 388:9-25) As a result, if a genome is cut with one enzyme it will generate a particular set of fragments, and if it is then cut with a different enzyme, it will generate a different set of overlapping fragments. (Tyagi Tr. at 125:20-127:3; Levy Tr. at 388:15-25)

53. Both Dr. de Winter and Dr. Sarkis testified that, depending on the experiment,

they would sometimes perform emulsion PCR of the test fragments alone, and other times they would mix test fragments together with adenovirus fragments. (Sarkis Tr. at 195:19-196:1; de Winter Tr. at 332:7-333:7)

54. Dr. Sarkis testified at trial that the 454 inventors wanted clonal amplification, so they designed their experiments with the goal of having a single effective copy per bead. (Sarkis Tr. at 182:24-183:21) Clonal amplification means amplifying a single DNA fragment in isolation from all others. (Sarkis Tr. at 217:5-23)

55. After December 2002, 454 scientists continued to perform experiments to optimize the conditions and develop a product that could be easily used by their customers. (Sarkis Tr. at 195:8-18)

H. The Poisson Distribution

56. The "Poisson distribution" is a statistical tool that can be used to predict the number of times that a given event occurs within a certain interval or physical space and is well-known and widely accepted. (Levy Tr. at 358:2-15) 454's expert, Dr. Tyagi, testified that the "Poisson distribution is [a] statistical distribution, basically, that scientists use when they want to deliver single cells into a well or single molecules in a reactor and so on." (Tyagi Tr. at 98:17-24) Using the Poisson distribution, it is possible to estimate the number of beads in a population that will be attached to more than one DNA fragment, to a single DNA fragment, and to no DNA fragments. (*See* Levy Tr. at 358:11-15)

57. The Poisson distribution has been repeatedly validated through empirical testing and experimental verification. (*Id.* at 361:4-15; Tyagi Tr. at 133:9-23) Dr. Tyagi explained: "The Poisson distribution stands on its own. It's always true," and "Poisson statistics are always

true, nobody is denying that." (Tyagi Tr. at 137:2-3, 138:25-139:1) The Poisson distribution is reliable evidence of what actually transpired during the experiments performed by 454's scientists. (Levy Tr. at 361:16-22, 498:13-24) The number of compartments present in a 454 emulsion PCR reaction can be calculated by knowing the diameter of the compartments and the volume of the aqueous solution. (*Id.* at 365:11-22) Knowing the number of compartments allows one to know if enough compartments have been generated to encapsulate all of the beads and all of the DNA fragments in the experimental setup. (*Id.*)

58. The Poisson distribution can be used to predict whether the emulsion PCR experiments performed by 454 contained some population of beads that had only a single DNA fragment attached. (*Id.* at 358:9-15) The December 20, 2002 experiment and each subsequent emulsion PCR experiment discussed hereinafter would be expected to conform to the Poisson distribution. (*Id.* at 359:23-360:11) Therefore, based on 454's experimental setups and the Poisson distribution, one can reliably conclude that those experiments included more than one microreactor with a single bead and the same single DNA fragment. (*Id.* at 365:4-366:15)

59. The sequencing data obtained from the 454 experiments further supports the finding that the Poisson distribution applies to those experiments. (*Id.* at 479:20-480:20, 481:24-482:6, 487:5-18, 490:18-24, 496:3-12) The 454 emulsion PCR experiments produced clear sequencing data showing individual sequencing reads were obtained. (*Id.* at 361:23-362:13, 363:5-13; *see also* ATX 1106 at 11) This means there must have been a population of emulsions in the experiment that had a single DNA fragment and a single bead. (Levy Tr. at 360:18-361:3, 361:23-362:13, 490:25-491:10) Drs. Sarkis and de Winter testified that their experiments produced multiple microreactors containing one bead with a single unique copy of the DNA

fragment, because clear sequencing results would not have been obtained if the microreactors contained multiple different fragments. (Sarkis Tr. at 240:10-241:24, 248:9-249:1; de Winter Tr. at 332:14-333:7, 345:13-19) Clear sequencing results were found in the experiments performed after December 20, 2002, including experiments that mixed test fragments with adenovirus fragments. (*See, e.g.*, Sarkis Tr. at 195:19-196:17, 212:12-213:11)

60. If there was more than a single fragment on a bead, then the sequencing data would not be clear – it would be muddled and would not map to a known sequence. (Levy Tr. at 362:14-20) If one can obtain sequencing data, that means there was only one sequence on the bead. (Tyagi Tr. at 546:6-8) Sequencing data also would not be produced if there were more than one bead per compartment. (Levy Tr. at 490:25-491:10)

I. 454 Experiments Were Reductions to Practice

61. 454 scientists performed a number of experiments between January and March of 2003, each of which qualifies as a reduction to practice, as explained below.

62. On January 14-15, 2003, Dr. Sarkis set up emulsion PCR reactions using a combination of adenovirus DNA and test fragments (TF4, TF6, TF7, and F6) with an input of 600,000 beads and 1.2 million molecules of DNA (two copies per bead) and successfully obtained sequencing results for the F6 test fragment from emulsion-PCR-generated beads. (Sarkis Tr. at 199:8-200:22; ATX 1105 at 112-13) Using this setup, based on a Poisson distribution, at least two microreactors would have contained a bead and a copy of the same F6 fragment. (Sarkis Tr. at 200:15-22; *see also* Levy Tr. at 359:23-360:11)

63. On January 22-23, 2003, Dr. Sarkis set up multiple emulsion amplification experiments on test fragments with a goal of creating microreactors containing one copy of DNA

fragment per bead. (*See* Sarkis Tr. at 202:15-203:13; ATX 1105 at 118) After January 23, 2003, his team generally used two copies per bead as input. (Sarkis Tr. at 204:7-10) One of the January 23 experiments showed successful amplification using emulsion PCR on a mixture of several different test fragments (TF1, TF2, TF3, TF4, TF5, TF6, TF7 and N7). (*Id.* at 203:14-204:18; ATX 1105 at 119) At least two microreactors in this experiment would have contained a single bead and a single copy of test fragment. (ATX 1105 at 119; *see also* Levy Tr. at 359:23-360:11) Dr. Sarkis testified that, with respect to this experiment, it was likely that "not only two, but thousands" of the microreactors would have contained a single bead and a single copy of the same DNA fragment, based on the Poisson distribution. (Sarkis Tr. at 204 at 12-18)

64. On January 28-31, 2003, Dr. Sarkis set up emulsion PCR reactions using a combination of adenovirus DNA and F6 test fragments with an input of 0.1, 2, and 10 copies per bead and successfully obtained sequencing results for the F6 test fragment from emulsion-PCR-generated beads. (Sarkis Tr. at 207:13-208:14; ATX 1105 at 141-42) Using this setup, and based on a Poisson distribution, at least two microreactors would have contained a single bead and a single copy of the same F6 fragment. (ATX 1115 ¶ 29; *see also* Levy Tr. at 359:23-360:11) These experiments were corroborated by another 454 scientist, Ms. Lanza, who referred to this experiment in her notebook on January 30, 2003 and included in it a copy of the same library distribution map found on page 143 of Dr. Sarkis's lab notebook. (Sarkis Tr. at 208:4-209:15; Lanza Tr. at 285:4-286:12; ATX 1105 at 143; ATX 1125 at 9; ATX 1126 ¶ 13)

65. On February 5, 2003, Dr. Sarkis performed emulsion PCR and obtained positive sequencing results from samples made by mixing 600,000 beads and 1,200,000 fragments of adenovirus DNA with linkers (an input ratio of two copies per bead). (Sarkis Tr. at

209:24-210:25; ATX 1106 at 1-2) The sample also contained F6 test fragments as a control. (ATX 1106 at 1-2; Levy Tr. at 358:16-359:12) Based on a Poisson distribution, at least two microreactors would have contained a single bead and a single copy of the same fragment. (Sarkis Tr. at 210:19-25) Dr. Levy testified that, according to the Poisson distribution, about 27% of the microreactors in this experiment would have had a single copy of the same DNA fragment attached to a single bead. (Levy Tr. at 358:16-359:22; *see also* Sarkis Tr. at 210:19-25)

66. On February 6, 2003, Dr. Sarkis performed emulsion PCR and obtained positive sequencing results from samples containing adenovirus DNA library mixed with TF6 test fragments. (Sarkis Tr. at 211:1-212:11; ATX 1106 at 11-12) Based on a Poisson distribution and the setup of this experiment, at least two microreactors would have contained a single bead and a single copy of the same fragment. (*Id.*; *see also* Levy Tr. at 359:23-360:11)

67. On February 7, 2003, Dr. Sarkis performed two emulsion PCR reactions and obtained positive sequencing results from samples containing beads mixed with adenovirus DNA library mixed with TF6 test fragments at a ratio of two copies per bead. (Sarkis Tr. at 212:12-214:8; ATX 1106 at 13-14, 19-20) Based on a Poisson distribution, at least two microreactors would have contained a single bead and a single copy of the same fragment in these experiments. (Sarkis Tr. at 213:5-11, 214:3-8; *see also* Levy Tr. at 359:23-360:11)

68. On February 10, 2003, Dr. Berka recorded in his lab notebook the notes from a meeting called by Kent Lohman, at which information on the progress of emulsion PCR was presented. (Berka Tr. at 304:11-17; ATX 1095 at 107; ATX 1113 ¶ 26) Dr. Berka noted that emulsion PCR yields about 10 million copies per bead and indicated "IT IS A GO!" (ATX 1095 at 107)

69. At this point, Dr. Sarkis believed he had optimized conditions for bead emulsion PCR and began preparing a document relating to "Best Practices" for "Polymerase Emulsion Chain Reaction." (Sarkis Tr. at 214:9-216:13; ATX 1102; ATX 1103; ATX 1115 ¶¶ 35-38) The purpose of the Best Practices document was to standardize methods at 454 for emulsion PCR. (ATX 1115 ¶ 35) Dr. Sarkis prepared the first draft with Dr. Ferland, who edited it on February 12-13, 2003. (*Id.*; Ferland Tr. at 268:14-271:22; ATX 1118 ¶¶ 2-5, 11-15; ATX 1102; ATX 1103)

70. The "Summary" section of the Best Practices document describes, *inter alia*, the six main steps of bead emulsion PCR: (1) template quality control, (2) PCR solution preparation, (3) binding of the item fragments to the DNA capture beads, (4) emulsion preparation, (5) amplification, and (6) recovery of the DNA template carrying beads from the emulsion. (Sarkis Tr. at 216:14-217:23; ATX 1102; ATX 1103) The summary further notes that "the emulsion format ensures the physical separation of the beads into 100 to 200 μm 'microreactors' within this single tube, thus allowing for clonal amplification of the template fragments." (ATX 1102 at 2)

71. The "Purpose" section of the Best Practices document repeats the concept of clonal amplification wherein "[s]ingle copies of the template species are hybridized to DNA capture beads, resuspended into complete PCR Amplification solution, and emulsified into microreactors (100 to 200 μm in diameter), after which PCR amplification generates 10^7-fold amplification of the initial template species." (Sarkis Tr. at 217:24-219:8; ATX 1102; ATX 1103)

72. On February 19, 2003, Dr. Sarkis performed two emulsion PCR experiments, and

obtained positive sequencing results from samples containing beads mixed with adenovirus DNA library fragments and PCR-generated test fragments TF6 and F6 at an input ratio of one copy per bead. (Sarkis Tr. at 219:9-220:10, 220:21-221:14; ATX 1106 at 79, 84-85) Based on a Poisson distribution, at least two microreactors would have contained a single bead and a single copy of the same fragment during these experiments. (Sarkis Tr. at 219:24-220:4, 221:10-14; *see also* Levy Tr. at 359:23-360:11)

73. On February 27, 2003, Dr. Sarkis inserted into his notebook an invention disclosure document entitled "Clonal DNA amplification and immobilization on emulsified microparticles." (Sarkis Tr. at 222:24-225:3; ATX 1106 at 107-12) The invention disclosure identifies Dr. Berka's notebook (ATX 1094 at 16) as the conception of the invention on June 7, 2002, and references reductions to practice based on, *inter alia*, documents dated December 19-20, 2002 (ATX 1097 at 2-6); December 31, 2002 (ATX 1097 at 7-9); January 14, 2003 (ATX 1105 at 112); February 4-8, 2003 (ATX 1105 at 147, 151-52; ATX 1106 at 1-45); and the February 12, 2003 Best Practices document (ATX 1102). The "Prior Art" section of the invention disclosure also identifies the Ghadessy and Sepp papers. (ATX 1106 at 111)

74. On March 7, 2003, Dr. Sarkis obtained successful results from emulsion PCR conducted on samples of mixed test fragments and single test fragments. (Sarkis Tr. at 221:15-222:23; ATX 1106 at 148-50) These experiments were set up at varying input ratios of 0.1, 0.5, 1, and 2 copies per bead. (ATX 1106 at 148) Based on a Poisson distribution, at least two microreactors would have contained a single bead and a single copy of the same fragment. (Sarkis Tr. at 222:16-23; *see also* Levy Tr. at 359:23-360:11)

75. On March 28, 2003, Dr. de Winter performed emulsion PCR and obtained

positive sequencing results from samples containing only a mixture of test fragments TF3, TF4, TF5, and TF7 at input ratios of 0.01, 0.1, and 1 copies per bead. (Sarkis Tr. at 225:4-227:6; de Winter Tr. at 334:16-19, 335:2-337:13; ATX 1122 at 84-85) Based on a Poisson distribution, at least two microreactors would have contained a single bead and a single copy of the same fragment. (Sarkis Tr. at 226:25-227:6; de Winter Tr. at 337:5-13; *see also* Levy Tr. at 359:23-360:11)

J. Corroboration of the Above-Described Reductions to Practice

76. Drs. Sarkis, Leamon, Berka and the other inventors worked collaboratively with each other and with other 454 employees – including Ms. Lanza, Dr. de Winter, and Mr. McDade – on bead emulsion PCR. (Sarkis Tr. at 179:5-9, 180:20-181:17, 185:6-186:8, 205:14-206:9, 208:4-209:15, 225:4-226:4; Lanza Tr. at 278:25-279:6, 280:21-288:9; *see also* ATX 1117, 1118, 1119, 1120, 1121, 1123, 1124, 1126)

77. Mr. McDade testified via declaration that he recalled discussing with Drs. Berka, Sarkis, and Leamon their idea for a method for analyzing nucleic acid sequences using bead emulsion PCR. (McDade Tr. at 264:14-267:2; ATX 1124 ¶¶ 10-13) Mr. McDade corroborated Dr. Sarkis's testimony, as well as the testimony of Drs. Berka and Leamon (via declaration), regarding the discussion recorded on page 16 of Dr. Berka's notebook (ATX 1094) on June 7, 2002. (ATX 1124 ¶¶ 10-13)

78. Mr. McDade also corroborated experiments conducted by Dr. Leamon from August to December 2002, and specifically recalled that Dr. Sarkis performed a bead emulsion PCR experiment that resulted in template amplification and sequenceable product just before Christmas in December 2002. (McDade Tr. at 267:3-267:18; ATX 1124 ¶¶ 14-15) Mr. McDade

also corroborated experiments conducted by Dr. Sarkis from January to February 2003 and recalled Dr. Sarkis creating the Best Practices document for bead emulsion PCR around that time. (McDade Tr. at 267:19-24; ATX 1124 ¶¶ 16-17)

79. Dr. Berka testified by declaration that in the 2002 to 2003 period it was common practice in the group to conduct formal and informal meetings to discuss various aspects of the projects that were ongoing; it was his practice to keep brief notes of the topics discussed at the meetings. (Berka Tr. at 302:16-20; ATX 1113 ¶ 22) Dr. Berka testified about several meetings that occurred in January and February 2003 relating to the emulsion PCR project and identified the people in the group from various sections who would have attended such meetings. (Berka Tr. at 303:5-306:16; ATX 1113 ¶¶ 24-30; ATX 1095 at 85, 90, 107-08)

80. Dr. Sarkis testified that before the 454 inventors came up with the idea for emulsion PCR, 454 was working on an alternative approach called PT-PCR ("pico-titer polymerase chain reaction"), in which microreactors were formed inside tiny wells on glass pico-titer plates rather than using water-in-oil emulsions. (Sarkis Tr. at 185:6-186:2; Lanza Tr. at 280:21-281:11) Ms. Lanza was working on PT-PCR amplification, and – because the two technologies had a lot of commonalities – she and Dr. Sarkis often collaborated. (Sarkis Tr. at 185:6-186:2) As Dr. Sarkis explained, he and Ms. Lanza were "sort of racing to find the right solution." (Sarkis Tr. at 186:1-2)

81. Ms. Lanza testified at trial regarding the almost daily collaboration she had with Dr. Sarkis and others about the emulsion PCR project in the January to February 2003 period. (Lanza Tr. at 280:21-288:9) Because they were comparing results, Ms. Lanza was aware of Dr. Sarkis's experiments, and in particular that he was performing emulsion PCR using adenovirus

libraries and F6 test fragments using low input ratios. (*Id.* at 288:10-289:1, 282:17-283:1)

82. Ms. Lanza testified that, by February 2003, everyone at 454 was generally aware of the success of emulsion PCR. (*Id.* at 288:10-289:16) Ms. Lanza noted that an experiment she was conducting on February 14, 2003 might have been her final PT-PCR run. (*Id.*; ATX 1125 at 37) Ten days later, on February 24, 2003, Ms. Lanza included a summary statement in her notebook indicating that "given [the] recent success of EPCR and PTPCR's contamination issues, all efforts will be on EPCR from now on." (ATX 1125 at 70)

83. Ms. Lanza began conducting experiments in March 2003 using the recipes for the emulsion oil and PCR mix from the EPCR Best Practices document prepared by Dr. Sarkis, which she pasted into her notebook. (Lanza Tr. at 289:17-290:15; ATX 1125 at 108-13, 116-17)

84. Dr. de Winter also ran emulsion PCR experiments using the procedure provided in the Best Practices document. (de Winter Tr. at 333:8-334:3; ATX 1122 at 74; ATX 1103) On February 18, 2003, Dr. de Winter inserted a graph in his notebook showing the amount of adenovirus sequenced with various samples, comparing Dr. de Winter's conditions, Dr. Sarkis's conditions, and Karrie Tartaro's (another 454 employee) conditions. (ATX 1122 at 74) The graph on page 74 of Dr. de Winter's notebook (ATX 1122) is the same as the graph on page 64 of Dr. Sarkis's notebook (ATX 1106) because Dr. Sarkis and Dr. de Winter were sharing information. (*Id.*)

85. The testimony of Dr. Ferland (ATX 1118), who worked on the Best Practices document, corroborates the testimony of Dr. Sarkis that he had conceived and reduced the invention to practice prior to February 12, 2003. (ATX 1102; ATX 1103)

86. The Invention Disclosure document and the documents referenced therein

corroborate a complete and clear conception and reduction to practice of the invention of the Count. (ATX 1097 at 2-6; ATX 1102; ATX 1103; ATX 1105 at 112, 118-34, 147, 151-52; ATX 1106 at 1-45; ATX 1131)

87. 454 demonstrated diligence at least from January 15, 2003 through 454's constructive reduction to practice on June 6, 2003. (ATX 252, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1123, 1126)

K. The '592 Application Describes and Enables the Method of the Count

88. The '592 provisional application describes and enables at least a single embodiment that falls within the scope of the Count. (Levy Tr. at 394:2-10)

89. The '592 provisional discloses the preamble of the Count. (ATX 1013 at 1:14-19)

1. The '592 Provisional Describes and Enables Step (a)

90. Use of a Type II restriction enzyme will generate two or more copies of the same fragment when used to digest multiple copies of a DNA target. (Tyagi Tr. at 82:14-83:2, 118:11-16; Levy Tr. at 368:17-369:10) Notably, the '592 provisional states:

> Suitable methods include . . . digestion with one or more restriction endonucleases (RE) to generate fragments of a desired range of lengths from an initial population of nucleic acid molecules. Preferably, one or more of the restriction enzymes have distinct four-base recognition sequences. Examples of such enzymes include, e.g., Sau3A1, MspI, and TaqI. . . . In other embodiments, the restriction enzyme is used with a type IIS restriction enzyme.

(ATX 1013 at 11:20-12:2)

91. A person of ordinary skill in the art would know that Type II restriction enzymes will produce the same set of fragments each time they are used to digest DNA. (Levy Tr. at

369:23-371:12; DTX 1 at 48 ("When a DNA sample is treated with one of these [Type II] enzymes, the same set of fragments is always produced, assuming that all of the recognition sites are cleaved.")) Dr. Tyagi testified that when a Type II restriction enzyme is used to conduct a complete digestion, the same set of fragments will always be obtained. (Tyagi Tr. at 123:18-25)

92. When using restriction endonucleases for DNA digestion, standard practice in the field is to conduct a complete digestion, so that all of the available restriction endonuclease recognition sites have been cleaved. (Levy Tr. at 371:17-372:10) Dr. Tyagi agrees the default use for restriction enzymes is to do a complete digestion. (Tyagi Tr. at 123:2-4) Thus, when a reference calls for a restriction endonuclease digestion, a person of ordinary skill would have understood that the DNA target should be digested to completion. (Levy Tr. at 372:7-10)

93. The '592 provisional does not contain any statements that suggest a partial digestion, i.e., a digestion that is not to completion, should be conducted. (Levy Tr. at 372:11-20) Dr. Tyagi agrees that nothing in the 454 applications says to do only a partial digestion with a Type II enzyme. (Tyagi Tr. at 125:11-14)

94. Given their common use in the field, a person of ordinary skill in the art would have understood how to use restriction enzymes to digest genomic DNA even without explicit guidance as to the protocol. (Levy Tr. at 371:9-16) Moreover, Dr. Tyagi agrees Type II restriction enzymes come with instructions explaining their use. (Tyagi Tr. at 122:6-14)

95. A person of ordinary skill in the art would not have used the conditions in Example 1 of the '592 provisional with a restriction enzyme. (Levy Tr. at 383:19-384:11) A person of ordinary skill would have known that restriction enzymes and DNase I are very different enzymes that require different conditions. (*Id.*)

96. The '592 provisional is clear that the template nucleic acid can be constructed from any source of nucleic acid, including tissue. (Levy Tr. at 373:3-10; ATX 1013 at 11:20-21 ("The template nucleic acid can be constructed from any source of nucleic acid, e.g., any cell, tissue, or organism . . . ")) A person of ordinary skill would have known that tissue is composed of more than one cell, which means it contains more than one copy of a genome. (Levy Tr. at 373:17-19) If restriction digestion was conducted on DNA isolated from a single diploid cell, which contains two copies of every gene, then two copies of the same DNA fragment would also be generated. (*Id.* at 381:15-25)

97. The '592 provisional also explains that the DNA can originate from a single-celled organism like a bacteria or virus. (*Id.* at 373:20-374:19; ATX 1013 at 8:12-13 ("DNA may be derived from any source, including . . . bacteria or [a] virus.")) A person of ordinary skill would have known that it is common laboratory practice to isolate bacterial or viral genomic DNA from a cell culture. (Levy Tr. at 374:20-377:7; DTX 18) Indeed, commonly available laboratory protocols isolate bacterial DNA from a culture of cells. (*Id.*) Those cultures contain trillions of cells (DTX 18 at 2.4.5 (stating 100 mL culture will have 10^8 to 10^9 cells/mL)), which means there will be trillions of copies of the genome available for isolation, and subsequent restriction digestion. (Levy Tr. at 376:13-377:2)

98. The '592 provisional states: "Template libraries can be made by generating a complementary DNA (cDNA) library from RNA, e.g., messenger RNA (mRNA)." (ATX 1013 at 12:3-4) Dr. Tyagi testified that converting mRNA to cDNA will result in the formation of multiple copies of the cDNA if multiple copies of the mRNA are present. (Tyagi Tr. at 127:4-7)

99. It is well-known to those of ordinary skill in the art that most mRNAs in a cell

exist in multiple copies. (Levy Tr. at 378:10- 379:5; DTX 11 at 107 ("Thousands of RNA transcripts can be made from the same DNA segment during each cell generation.")) Each mRNA can serve as a template for reverse transcription, which converts RNA into DNA. (Levy Tr. at 378:17-24, 381:2-4) The result is that multiple copies of an identical DNA may be generated, even when DNA is isolated from a single cell. (*Id.* at 378:2-9, 381:2-14)

100. In addition, cDNA libraries are typically generated by using RT-PCR. (*Id.* at 378:17-379:5) The '592 provisional describes the use of RT-PCR to convert RNA to DNA. (*Id.* at 380:11-23; ATX 1013 at 64:6-8 ("While DNA is the preferred template, RNA and PNA may be converted to DNA by known techniques such as random primed PCR, reverse transcription, RT-PCR, or a combination of these techniques.")) RT-PCR is a process where reverse transcription is coupled to a PCR amplification step, which will result in the formation of millions of copies of the DNA. (Levy Tr. at 380:24-381:8) Using this process, even if there is only a single mRNA present in a cell, millions of copies of DNA would be generated. (*Id.* at 381:9-14) Dr. Tyagi testified that use of RT-PCR will generate multiple copies of a cDNA from a single mRNA. (Tyagi Tr. at 127:8-14)

101. PCR or RT-PCR amplification of DNA is a method of fragmenting permitted by step (a) of the Count. (Levy Tr. at 503:1-21) Indeed, that is the method of fragmenting disclosed in the '690 application. (*Id.*) Moreover, if the PCR or RT-PCR amplification products are subsequently fragmented with restriction enzymes, this would generate two or more copies of the same DNA fragment. (*Id.* at 465:11-466:1)

2. The '592 Provisional Describes and Enables Step (b)

102. The '592 provisional explains that the capture of beads and DNA in

microemulsions will follow the Poisson distribution, and result in a subset of emulsions with single beads hybridized to single DNA fragments. (Levy Tr. at 389:25-390:15; ATX 1013 at 21:16-19)

103. The '592 provisional contains an extensive discussion on how to make and use emulsions. (ATX 1013 at 29:28-31:4, 85:25-86:18)

104. A person of ordinary skill in the art would have understood the '592 provisional to teach that DNA can be harvested from almost any source, and would not be limited to only a single cell. (Levy Tr. at 372:21-373:16) Dr. Tyagi's opinion that the '592 provisional teaches that only "a cell" would be used as a starting source of material for step (a) of the Count ignores that the same quoted sentence from the '592 provisional teaches that a template can be harvested from tissue or organisms. (Tyagi Tr. at 75:16-76:8; Levy Tr. at 377:14-378:1)

3. The '592 Provisional Describes and Enables Steps (c) and (d)

105. The '592 provisional discloses the amplification step covered by step (c). (*See, e.g.*, ATX 1013 at 30:8-13, 31:6-29)

106. The '592 provisional discloses detecting amplified copies, as described in step (d). (*See, e.g.*, *id.* at 32:15-27)

L. The '071 Application Describes and Enables the Method of the Count

107. The '071 provisional describes and enables an embodiment within the scope of the Count. (Levy Tr. at 407:3-10)

108. The '071 provisional satisfies the preamble of the Count by describing methods of sequencing. (*Id.* at 407:11-408:3; ATX 1015 at 38 (pyrophosphate sequencing))

1. The '071 Provisional Describes and Enables Step (a)

109. A person of ordinary skill would have understood that the '071 provisional describes and enables step (a) of the Count. (Levy Tr. at 409:5-19) In particular, the '071 provisional states at page 40: "DNA isolation prior to sequencing is performed by any of several commercially available methods. Fragmentation can be performed by one of many methods, including physical and sonic shearing, DNA restriction endonuclease digestion, and nuclease treatment." (ATX 1015 at 40)

110. Dr. Tyagi agreed that the language on page 40 of the '071 provisional could describe step (a). (Tyagi Tr. at 531:3-11)

111. All commercially available kits for DNA isolation at the time the '071 provisional was filed were designed to isolate DNA from bulk samples, e.g., tissue samples or cell cultures. (Levy Tr. at 409:20-410:10; Tyagi Tr. at 553:11-21; DTX 16; DTX 20; DTX 21) There were no well-known, commercially available kits for the isolation of DNA from a single cell at the time the '071 provisional was filed. (Levy Tr. at 413:25-414:4) Thus, a person of ordinary skill would have understood that the '071 provisional describes preparing DNA samples with multiple copies of a given genome. (*Id.* at 418:11-20)

112. The '071 provisional does not disclose any methods or techniques for isolating DNA from a single cell. (*Id.* at 414:5-8) A person of ordinary skill would not have understood from the '071 provisional that DNA should be isolated from a single cell. (*Id.* at 414:9-13) Indeed, because it teaches the use of commercially available kits, the '071 provisional suggests the opposite. (*Id.*)

113. Isolating DNA from a single cell has disadvantages associated with it. (*Id.* at

414:14-415:2) For example, because there were then no commercially available kits to do it, one would have to design a protocol to isolate the DNA. (*Id.*) In addition, there is only one copy of the genome available, leaving a very limited amount of material with which to work. (*Id.*) If any DNA were lost, it could not be sequenced. (*Id.*) For these reasons, a person of ordinary skill in the art would not work with a single cell unless she had to do so. (*Id.*)

114. The '071 provisional also describes fragmenting DNA with restriction enzymes. (*Id.* at 415:3-19; ATX 1015 at 40) The use of restriction enzymes to fragment DNA isolated with commercially available methods results in the generation of two or more identical DNA fragments. (Levy Tr. at 415:12-19)

115. A person of ordinary skill in the art would have understood reference to restriction endonuclease to be a reference to Type II restriction enzymes. (*Id.* at 415:24-416:13) Both Drs. Levy and Tyagi testified that Type II restriction enzymes were the only commercially available restriction enzymes when the '071 provisional was filed. (Levy Tr. at 416:4-13; Tyagi Tr. at 550:21-23) Type II restriction enzymes were also the only type of restriction enzymes used in molecular biology laboratory applications. (Levy Tr. at 369:17-22; DTX 1 at 48 ("The importance of the type II restriction endonucleases for gene cloning cannot be overstated.")) Dr. Tyagi testified that a person of ordinary skill would have used Type II restriction enzymes to digest DNA. (Tyagi Tr. at 121:5-8)

116. The '071 provisional also describes generating template for SNP analysis via PCR. (Levy Tr. at 417:12-418:10; ATX 1015 at 76 ("Using primers targeting sequences in close proximity to known SNP-containing regions of interest on chromosome 21, we can amplify individual, large fragments and load them onto our capture beads in Eppendorf tubes . . . .”))

PCR amplification generates millions of copies of that fragment. (Levy Tr. at 418:8-10)

2. The '071 Provisional Describes and Enables Step (b)

117. A person of ordinary skill would have understood that the '071 provisional describes and enables step (b) of the Count. (*Id.* at 418:21-419:3) For example, the '071 provisional states:

> A second approach to amplifying and capturing both strands will be to amplify the fragment library offline in a single tube using oil and surfactant-based emulsions to encapsulate the capture beads, template and PCR reaction mix. This approach will maintain the clonality of the amplification . . . . The average size of the emulsion capsules must be optimized to maximize the number of single beads containing single strands of DNA, that can be incorporated within a single emulsion volume. An adequate volume-to-bead ratio must be maintained in order to insure a maximum number [of] single bead capsules.

(ATX 1015 at 46-47)

118. The paragraph quoted above (from pages 46 to 47 of the '071 provisional) describes emulsion PCR. (Levy Tr. at 419:24-420:2) It also describes using the fragment library that was generated according to the methods described on page 40, i.e., step (a), as template. (*Id.* at 420:9-15) It further describes all of the requirements of step (b), i.e., using emulsions to capture beads, template, and PCR mix. (*Id.* at 420:16-20)

119. The '071 provisional explains that there should be a single DNA fragment per emulsion. (*Id.* at 420:21-421:13, 422:4-8; ATX 1015 at 46-47 ("This approach will maintain the clonality of amplification . . . . [Emulsions] must be optimized to maximize the number of single beads containing single strands of DNA, that can be incorporated within a single emulsion volume."))

120. The '071 provisional provides guidance on the parameters that need to be considered in setting up the emulsion PCR. (Levy Tr. at 421:14-19) In particular, it notes the average size of the capsules needed to make sure there is a single bead and a single template per emulsion. (*Id.* at 421:20-422:8; ATX 1015 at 46-47) With these disclosures in mind, a person of ordinary skill in the art would have looked to literature available at the time for details on how to optimize the emulsion size. (Levy Tr. at 422:9-16)

121. Tawfik and Griffiths published an article in Nature Biotechnology – a well-known journal to persons of ordinary skill in the art – that involves making emulsions for the encapsulation of biological reactions. (*Id.* at 422:17-423:19; DTX 23) The publication contains detailed guidance on how to form the emulsion compartments used in the reported experiments. (Levy Tr. at 423:20-424:12; DTX 23 at 655 (under "Experimental Protocol" and subheading "Emulsified Reactions")) For example, the Tawfik and Griffiths paper provides precise amounts of specific reagents to use, identifies the temperature to use, and details the mixing procedure. (DTX 23 at 655)

122. The same paper also explains that "[t]he precise stirring setup can greatly affect droplet size." (Levy Tr. at 424:13-19; DTX 23 at 655 under "Experimental Protocol" and subheading "Emulsified Reactions")) A patent by Tawfik and Griffiths that issued prior to the '071 provisional filing date also explains that "the size of the emulsion microcapsules may be varied simply by tailoring the emulsion conditions used to form the emulsion according to the requirements of the selection system." (DTX 24 at 11:29-31) From these disclosures, a person of ordinary skill would have understood the size of the emulsions reported in the Tawfik and Griffiths paper could have been controlled by manipulating the emulsion conditions and the

stirring setup. (Levy Tr. at 427:4-17)

123. Ghadessy et al. published a paper in PNAS – a well read and respected journal – that modified the emulsions reported in Tawfik and Griffiths. (*Id.* at 427:18-430:5; DTX 33 at 4553, heading "Emulsification of CSR," referring to reference (16), which is identified on page 4557 as DTX 23) The Ghadessy paper states:

> We used the recently described water-in-oil emulsions (16 [DTX 23]) but modified the composition of the surfactants as well as the water-to-oil ratio. This modification greatly increased the heat stability and allowed PCR yields in the emulsion to approach those of PCR in solution. Compartments had average diameters of 15 μm and proved heat-stable . . . .

(DTX 33 at 4553, below "Principles Underlying CSR")

124. By modifying the emulsion of DTX 23, the Ghadessy authors were able to use the emulsions for PCR amplification. (Levy Tr. at 430:20-431:5) By slowing down the speed of the stir bar, the authors were also able to significantly increase the size of the emulsions reported in DTX 23. (*Id.* at 431:6-14, 453:4-17) The Ghadessy paper demonstrates that size optimization of emulsions is a straightforward process. (*Id.* at 431:15-20)

125. A person of ordinary skill in the art would have been familiar with DTX 23, DTX 24, and DTX 33 at the time the '071 provisional was filed. (*Id.* at 432:14-23) The JHU '690 application references DTX 23 and DTX 33 as examples of how to form emulsions. (ATX 1003 ¶ 44 (reference 14 is Tawfik and Griffiths (DTX 23) and reference 15 is Ghadessy et al. (DTX 33)) Using those references, a person of ordinary skill could have manipulated the size of the emulsions reported in DTX 23 or DTX 33 to encapsulate a bead without undue experimentation. (Levy Tr. at 432:5-13) There is no conceptual difference between encapsulating a bacterium or a

bead. (*Id.* at 431:21-432:4)

3. The '071 Provisional Describes and Enables Steps (c) and (d)

126. Step (c) of the Count requires amplifying the fragment of step (a) in the microreactor. (*Id.* at 433:15-20) The '071 provisional describes step (c) of the Count because it describes emulsion PCR. (*Id.* at 433:12-25; ATX 1015 at 46-47)

127. The '071 provisional describes step (d) because it describes pyrophosphate sequencing. (Levy Tr. at 434:1-16; ATX 1015 at 38) In order for pyrophosphate sequencing to work, the DNA has to have been amplified. (Levy Tr. at 434:6-9)

128. The '071 provisional contains no indication that a partial digestion should be performed, as opposed to a complete digestion. (ATX 1015 at 40)

M. The '240 Application Describes and Enables the Full Scope of the Count

129. The '240 application describes and enables the full scope of step (a) of the Count because it describes and enables making genomic DNA libraries or cDNA libraries derived from any population of nucleic acids. (Levy Tr. at 394:11-395:7; ATX 1001 at 3:25-28) A person of ordinary skill in the art would have understood that methods of generating those libraries involve the formation of more than one copy of a particular DNA fragment. (Levy Tr. at 395:8-15)

130. The '240 application also incorporates by reference the '071 and '592 provisionals.[7] (*Id.* at 396:6-15; ATX 1001 at 1:3-6) It also incorporates by reference U.S. Patent No. 7,323,305, which contains the entire disclosure of the '592 provisional. (Levy Tr. at 396:16-398:12, 400:11-20; ATX 1001; DTX 12; DTX 13)

[7]Given that the '071 and '592 applications describe and enable the preamble, the '240 application does as well because it incorporates these disclosures by reference.

131. The '240 application describes delivery of single-stranded and double-stranded DNA to the microreactors by describing pre-hybridizing beads via oligonucleotide primers attached to the beads. (Levy Tr. at 404:10-15; ATX 1001 at 7:16-8:31, 25:6-26:30) The '592 and '071 provisional applications also describe delivery of DNA pre-hybridized to a bead, so those applications also describe the delivery of single-stranded and double-stranded DNA to the microreactor. (ATX 1013 at 21:1-10; ATX 1015 at 46-47) When the DNA fragment is pre-hybridized to the bead via that primer, it forms a short region of double-stranded DNA. (Levy Tr. at 404:16-22) The other portion of the fragment is single-stranded. (*Id.* at 404:23-24) Thus, a partially single-stranded and partially double-stranded DNA fragment is delivered to the microreactor. (*Id.* at 404:25-405:3)

132. The only difference between delivery of a single-stranded DNA fragment pre-hybridized to a bead and a double-stranded DNA fragment not pre-hybridized is the omission of the pre-hybridization step. (Tyagi Tr. at 139:5-10; Levy Tr. at 405:17-22) The components are still delivered the same way. (Levy Tr. at 405:17-22, 406:16-20, 475:10-24)

133. Very little, if any, experimentation would be required to deliver the double-stranded DNA, as opposed to the single-stranded DNA fragment. (Levy Tr. at 405:25-406:20, 437:15-21) Dr. Tyagi's speculation that delivering double-stranded DNA separately from a bead would be different from delivering DNA pre-hybridized to a bead is not based on any actual experimental evidence. (Tyagi Tr. at 547:16-548:5)

134. Dr. Levy explained that modification of the parameters necessary to successfully form a microemulsion could be done in a day. (Levy Tr. at 456:4-14) Dr. Levy further opined that modification of those parameters is "extremely simple," and would "absolutely not" require

undue experimentation. (*Id.* at 501:17-502:1)

135. Dr. Tyagi testified that delivery of one DNA fragment and one bead into each of a plurality of microreactors could be confirmed using "statistical probabilities." (Tyagi Tr. at 60:12-15) The '240 application uses statistical probabilities to confirm delivery of DNA and beads to the microreactors. (ATX 1001 at 16:12-17:27)

N. JHU is Not Entitled to a Priority Date Earlier than June 5, 2003

136. None of the priority evidence JHU provides demonstrates that JHU had conceived of all the elements of the Count prior to June 5, 2003, including: (1) delivering a plurality of molecules of the same fragment of DNA into microreactors; (2) any type of emulsion; (3) any microreactor; (4) having a single bead in a microreactor; and (5) having a single molecule of a DNA fragment in a microreactor.

137. JHU cites isolated testimony and documents relating to PCR pre-amplification outside of an emulsion, or optimization of emulsion conditions, but there is no evidence the JHU inventors had the concept of putting template into the emulsion, amplifying in emulsion, and detecting amplification products from the emulsion, which are all required elements of the Count.

138. ATX 2043 and/or ATX 2081 are not evidence for performing emulsion PCR, prior to June 5, 2003, as these documents contain no explanation, nor is there any non-inventor corroborating testimony explaining the experiment underlying the data, or the computer files.

139. Neither the Dressman publication (ATX 2026) nor any of its drafts can corroborate work done prior to the date the manuscript was completed, and its existence has only been proven by JHU as of June 5, 2003.

140. The only non-inventor testimony JHU has cited are the declarations of Leslie Meszler (ATX 2029) and Jason Briody (ATX 2081).

141. Declarant Meszler merely testifies regarding calendaring time for inventor Dressman to use a flow cytometer in the Cell Imaging Core at JHU and the charges for that use, and regarding a listing of data folders from a MacIntosh computer used at the Cell Imaging Core in 2003. (ATX 2029)

142. Declarant Briody likewise testifies merely to a listing of data folders from the MacIntosh computer and associated metadata. (ATX 2081)

143. Neither of the corroborating declarations includes any information as to the experiments that were being performed by inventor Dressman in the Cell Imaging Core, nor do they address any aspect of the invention of the Count.

144. The January 29, 2003 email from Dr.Vogelstein to Dr. Kinzler (both inventors) does not refer to various required elements of the Count: (1) delivering a plurality of molecules of the same fragment of DNA into microreactors; (2) any type of emulsion; (3) any microreactor; (4) having a single bead in a microreactor; or (5) having a single molecule of a DNA fragment in a microreactor. (ATX 2039) Furthermore, Dr. Vogelstein admits that the attachment to the email relates to a non-emulsion format. (ATX 2034 ¶ 12) Moreover, the January 29, 2003 email is not corroborated by a non-inventor.

145. The February 10, 2003 PCR amplification of the Calpain gene from a heterozygous patient source provides no indication as to the future use of the amplification products, and thus, no evidence was submitted that the Calpain amplification products were intended for use in emulsion PCR. Moreover, none of the inventor testimony regarding this

experiment is corroborated. (ATX 2040, ATX 2034 ¶¶ 27-28, ATX 2051 ¶ 29; ATX 2080 ¶ 5)

146. JHU's contention that Dr. Dressman used the amplified Calpain gene for a bead emulsion experiment on February 25, 2003 is based solely on uncorroborated inventor testimony. Moreover, the cited pages of Dr. Dressman's notebook do not even refer to using an emulsion, much less to microreactors containing a single DNA fragment and a single bead. (ATX 2051 ¶ 29; ATX 2036 at 39)

147. JHU cites other isolated testimony and documents that relate to PCR pre-amplification outside of an emulsion, or optimization of emulsion conditions, as alleged evidence of conception in February 2003, but there is no corroborated evidence that the inventors had the concept of putting template into the emulsion, amplifying in emulsion, and detecting amplification products from the emulsion, which are all required elements of the Count.

148. There is no corroborated evidence that JHU performed bead emulsion PCR on March 10 and March 31, 2003, using a single bead and a single template DNA in microreactors formed in a water-in-oil emulsion. (ATX 2024; ATX 2032; ATX 2051 ¶¶ 26-55, ATX 2079 ¶¶ 32-39)

149. With respect to the March 10 experiments, there is no evidence of: (1) multiple copies of a particular template (i.e., generated as by PCR); (2) a single template; or (3) a single bead per compartment, as required by the Count. (ATX 2036 at 71)

150. With respect to the March 31 experiments, the cited evidence refers only to a PCR product, not to its source. (*Id.* at 99) Furthermore, there is no discussion and/or evidence of a single DNA template molecule and a single bead in a water-in-oil emulsion microreactor, and there is no evidence that the product was detected, as required by the Count. (*Id.*)

151. The last dated page in Dr. Dressman's notebook is from April 1, 2003.

152. JHU cannot rely on ATX 2081 as evidence for performing emulsion PCR experiments, prior to June 5, 2003, because it is merely a listing of files recovered from a Macintosh computer, suggesting that Dr. Dressman had the JHU Cell Imaging Core perform some sort of flow cytometery, but there is no evidence in ATX 2081 regarding what was analyzed in any of those flow cytometry runs. Moreover, there is no corroborating evidence regarding what was analyzed in any of those flow cytometry runs.

153. JHU cannot locate information allegedly contained in a three-ring binder of Dr. Dressman to explain what experiments were listed in ATX 2081. (ATX 2079 ¶¶ 4-5)

154. Likewise, JHU cannot rely on ATX 2043 as representing data associated with emulsion PCR experiments, because there is no explanation in the document or in any non-inventor corroborating testimony that explains what type of experiment the data represents. There is no evidence that it represents bead emulsion PCR or using microreactors containing a single bead and a single template DNA.

155. JHU cannot rely on ATX 2042 as evidence of another alleged bead emulsion experiment prior to May 12, 2003, because it is an undated draft of a manuscript that is not corroborated by non-inventor testimony. (ATX 2034 ¶¶ 31-38; ATX 2080 ¶ 6-7)

156. JHU has not provided evidence that there was an emulsion PCR experiment performed on May 20, 2003, because JHU relies solely on uncorroborated inventor testimony and an undated draft of a manuscript that is not corroborated by non-inventor testimony. (ATX 2034 ¶¶ 31-33; ATX 2051 ¶ 58; ATX 2079 ¶¶ 27, 29; ATX 2080 ¶ 6)

157. The JHU inventors use hindsight to attempt to reconstruct the evidence they could

not provide, by citing to the Dressman publication (ATX 2026) and proposing dates on which the work reflected in the paper might have occurred. However, neither the Dressman publication (ATX 2026) nor any of its uncorroborated drafts (ATX 2042 and ATX 2097 through 2114) can corroborate work done prior to the date the manuscript was completed, and its existence has only been proven by JHU as of June 5, 2003.

158. JHU has not provided any evidence that it continued to work on bead emulsion after the June 5, 2003 manuscript.

DISCUSSION

I. PRIORITY

A. Legal Standards

JHU, as the junior party to the Interference, must show priority by a preponderance of the evidence.[8] *See Brown v. Barbacid*, 276 F.3d 1327, 1332 (Fed. Cir. 2002) ("*Brown I*"). "Priority of invention and its constituent issues of conception and reduction to practice are questions of law predicated on subsidiary factual findings." *Singh v. Brake*, 317 F.3d 1334, 1340 (Fed. Cir. 2003). "Priority of invention 'goes to the first party to reduce an invention to practice unless the other party can show that it was the first to [1] conceive the invention and [2] that it exercised reasonable diligence in later reducing that invention to practice.'" *Brown I*, 276 F.3d at 1337 (quoting *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993)); *see also Brown v. Barbacid*, 436 F.3d 1376, 1378 (Fed. Cir. 2006) ("*Brown II*") ("The party that is first to conceive the

[8]An applicant who challenges an issued U.S. patent during an interference must prove priority by clear and convincing evidence. *See Bruning v. Hirose*, 161 F.3d 681, 684 (Fed. Cir. 1998). The patents in this case were co-pending and had not yet issued at the time the Interference was initiated, so the preponderance of the evidence standard governs. *See id.* at 686.

invention in interference, if last to reduce the invention to practice, is entitled to the patent based on prior conception if, as first to conceive, he exercised reasonable diligence from a time before the other party's conception date to his own reduction to practice date.").

1. Conception

"Conception is the formation, in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice." *In re Steed*, 802 F.3d 1311, 1320 (Fed. Cir. 2015) (internal quotation marks omitted). To show conception, "a party must show possession of every feature recited in the count, and that every limitation of the count must have been known to the inventor at the time of the alleged conception." *Coleman v. Dines*, 754 F.2d 353, 359 (Fed. Cir. 1985).

When proving conception, the inventor "must provide independent corroborating evidence in addition to his own statements and documents." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1375 (Fed. Cir. 2009) (internal citation omitted). Corroboration is subject to a "rule of reason" analysis. *Reese v. Hurst*, 661 F.2d 1222 (C.C.P.A. 1981). "Accordingly, a tribunal must make a reasonable analysis of all of the pertinent evidence to determine whether the inventor's testimony is credible." *Kridl v. McCormick*, 105 F.3d 1446, 1450 (Fed. Cir. 1997).

2. Reduction to Practice

"A reduction to practice can be either a constructive reduction to practice, which occurs when a patent application is filed, or an actual reduction to practice." *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998). "In order to establish an actual reduction to practice, the inventor must prove that: (1) he constructed an embodiment or performed a process that met all

the limitations of the interference count; and (2) he determined that the invention would work for its intended purpose." *Id.*

When proving a constructive reduction to practice, "all that is necessary for a party to be entitled to benefit of an earlier filed application for priority purposes is compliance with 35 U.S.C. § 112 with respect to at least one embodiment within the scope of the count." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1362 (Fed. Cir. 2006) (internal brackets and quotation marks omitted). In *Hunt v. Treppschuh*, 523 F.2d 1386, 1389 (C.C.P.A. 1975), the Court of Customs and Patent Appeals distinguished between requirements under § 112 for applications serving as bases for priority, on the one hand, and interfering applications which have the potential to ripen into issued patents, on the other:

> Hunt's parent application is relied upon as a prior constructive reduction to practice; whereas in [*Smith v. Horne*, 450 F.2d 1401 (C.C.P.A. 1971)], the disclosure was relied upon for a right to make the count. In the latter situation the requirements of the first paragraph of 35 U.S.C. § 112 must be satisfied for the full scope of the count. In the former, however, the § 112, first paragraph requirements need only be met for an embodiment within the count.

As applied to this case, the holdings in *Falko* and *Hunt* require 454's '592 and '071 applications – which 454 relies on only as bases for priority – to describe and enable at least one embodiment within the scope of the Count. By contrast, 454's '240 application must describe and enable the ***full scope*** of the Count, as 454 desires to obtain (in fact, retain) patent rights to the claims set out in the '240 application (which is now the issued '305 patent).

B. 454's Conception and Reduction to Practice

1. 454 Conceived of the Invention by December 20, 2002

Considering the evidence in its entirety, the Court concludes that 454 has proven by a preponderance of the evidence that it had a "definite and permanent idea of the complete and operative invention," *Steed*, 802 F.3d at 1320, by no later than December 20, 2002. (*See* FF35-55)[9] A group of the inventors initially discussed the idea for a method for analyzing nucleic acid sequences using bead emulsion PCR on June 7, 2002, as evidenced in Dr. Berka's lab notebook and as testified to by Drs. Sarkis and Leamon. (ATX 1094 at 16; Sarkis Tr. at 180:8-183:5; ATX 1114 ¶ 17) Dr. Berka's lab notebook includes a depiction of the basic concept of the invention, showing a PCR reaction involving individual bead-fragment combinations in a water-in-oil emulsion. (ATX 1094 at 16)

Initial experiments performed by Dr. Leamon revealed problems with emulsions "crashing" before amplification or sequencing could be performed. (FF39) However, later experiments improved the stabilization of the emulsions, permitting Dr. Sarkis to complete steps (a) through (c) of the Count in an experiment on December 20, 2002. (FF39, 41-44) Dr. Sarkis used test fragments that had been prepared by Mr. Altman, who testified that the test fragments he had had been PCR amplified and, therefore, comprised multiple copies of the same DNA fragment, in compliance with step (a). (FF44-48) Dr. Sarkis testified that the goal of the 454 inventors was clonal amplification, meaning their goal was to have a single effective copy per bead per microreactor, in compliance with step (b). (FF54) Dr. Sarkis and Mr. Altman had

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[9]Citations to the Court's Findings of Fact, which are provided earlier in this Opinion, are in the following format: "FF[paragraph number(s)]."

previously sequenced the test fragments in separate experiments, in compliance with step (d). Although sequencing was not completed on December 20, 2002 on the amplified copies of DNA, the ultimate goal of the 454 scientists was to develop a procedure that would include step (d) of the Count (and, again, they had done step (d) of the Count earlier and, plainly, still had possession of step (d)). (*See* Sarkis Tr. at 201:1-11) Dr. Sarkis's testimony, which the Court found to be credible, in combination with all of the other relevant evidence, indicates that 454 conceived of the invention by no later than December 20, 2002.

454's conception was corroborated by non-inventor testimony. (*See* FF56-87) In particular, Mr. McDade corroborated the discussions of June 7, 2002. (FF77) In addition, Mr. McDade specifically recalled that Dr. Sarkis performed a bead emulsion PCR experiment that resulted in template amplification and sequenceable product just before Christmas in December 2002. (FF78) Ms. Lanza recorded in her lab notebook the sequence of one of the PCR-generated test fragments used by Dr. Sarkis in his December 20, 2002 experiment. (FF47) Mr. Altman testified that he PCR amplified the test fragments used by Dr. Sarkis in his December 20, 2002 experiment. (FF46)

454's conception is further corroborated by testimony regarding the applicability of the Poisson distribution to Dr. Sarkis's December 20, 2002 experiment. (*See* FF56-60) The Poisson distribution may be relied on as evidence of what actually transpired during the experiments performed by 454's scientists, including the December 20, 2002 experiment. (Levy Tr. at 361:16-22, 498:13-24) The Court credits Dr. Levy's testimony and finds his discussion of the Poisson distribution to establish that it is highly probable that Dr. Sarkis's December 20, 2002 experiment resulted in more than one microreactor containing a bead and the same DNA

fragment, satisfying the limitations of step (b) of the Count.

JHU's criticisms of 454's experimental evidence from the December 20, 2002 experiment are contradicted by documentary evidence and testimony from 454's witnesses, all of whom the Court found to be credible. (*See, e.g.*, D.I. 110 at 31) (alleging there is "[n]o evidence of amplification of test fragments according to step (c)," when evidence shows that opposite is true (*see* ATX 1105 at 95-96)) Regarding conception specifically, JHU alleges that the 454 inventors failed to appreciate step (a) of the Count and, therefore, did not conceive of the invention by December 20, 2002. (*See* D.I. 110 at 28-32) The Court disagrees. Dr. Sarkis knew the test fragments were PCR-generated and included them in his microemulsion experiment, according to step (a) of the Count. (Sarkis Tr. at 194:11-15)[10] This satisfies step (a) of the Count as it plainly involved generating a plurality of molecules of a fragment of DNA.

JHU focuses on the fact that 454 was ultimately interested in analyzing adenovirus fragments that were not generated in such a way that would have created more than one of the same fragment according to step (a). (*See id.* at 28-29) Regardless of what the ultimate goal of 454 was, as a company, the evidence shows that Dr. Sarkis understood himself to be performing step (a) of the Count by including test fragments in his microemulsion experiment on December 20, 2002. Step (a) was known by, and in the possession of, Dr. Sarkis as of that date. JHU's

[10]JHU insists that both "conception and reduction to practice 'require contemporaneous recognition and appreciation of the limitations of the claimed invention' not just fortuitous inherency." (D.I. 115 at 29) (quoting *Mycogen Plant Sciences, Inc. v. Monsanto Co.*, 252 F.3d 1306, 1314 (Fed. Cir. 2001)) However, as 454 argues, the Federal Circuit – citing *Mycogen* – has held that in an interference a prior inventor need not "demonstrate that [she] recognized the exact language of the ultimate count" but "only the subject matter of the invention." (D.I. 118 at 27) (citing *Henkel Corp. v. P&G*, 485 F.3d 1370, 1375 (Fed. Cir. 2007))

insistence that it and 454 had different aims and were pursuing different inventions[11] does nothing to undermine the Court's findings that 454 conceived of the invention of the Count by December 20, 2012[12] – ***even if at some earlier date the parties' initial intentions differed.***

JHU raises additional challenges to 454's conception of the invention which are addressed below in connection with the Court's analysis of 454's reductions to practice.

2. 454 Actually Reduced the Invention to Practice by January 15, 2003

454 has proven by a preponderance of the evidence that it actually reduced the invention of the Count to practice, starting at least by January 15, 2003. (*See* FF61-87) For example, from January 14 to 15, 2003, Dr. Sarkis set up emulsion PCR reactions using a combination of adenovirus DNA and test fragments (TF4, TF6, TF7, and F6) with an input of 600,000 beads and 1.2 million molecules of DNA (two copies per bead) and successfully obtained sequencing results for the F6 test fragment from emulsion-PCR-generated beads. (FF62) The F6 fragments

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[11]According to JHU, "[t]he objective of the JHU application is to find mutations in specific portions of the genome," which "requires generating multiple copies of a fragment of the genome" through two steps: "pre-amplification," which is step (a) of the Count, and "emulsion amplification," which is step (c). (D.I. 110 at 1) JHU continues by contending that the objective of 454's application, by contrast, "is to assemble genome sequences from snippets of the genome," which entails "the genome be[ing] fragmented into many overlapping pieces." (*Id.*) In JHU's telling, the "use of a second or 'pre-amplification' step is counter-productive to the objective of the 454 application as it generates multiple copies of the same fragment," whereas the whole point of 454's invention is to "piece[] together" multiple fragments "to assemble the entire genome." (*Id.*; *see also* D.I. 115 at 18 ("[JHU] has produced substantial evidence at trial that not only are the methods described in the [454] '071 and '592 Applications different from JHU's applications, but that the reason for that difference is due to the different goals and objectives of the applications – gene sequencing v. detection of gene mutations – which shows the methods are not obvious variants of one another."))

[12]This is months before JHU's conception – which occurred no earlier than June 5, 2003 – meaning that 454 both conceived the invention of the Count before JHU did and then began using reasonable diligence to reduce to practice before JHU even conceived of the invention. *See Brown II*, 436 F.3d at 1378.

satisfy step (a) of the Count, because they were generated by PCR, as Mr. Altman explained. (FF46) According to Dr. Levy's testimony, which the Court credits, this experiment would have produced at least two microreactors (i.e., a plurality) each containing one bead and one of the same F6 test fragments, in accordance with step (b) of the Count. (Levy Tr. at 359:23-360:11) The F6 fragments, bound to beads, were then amplified and sequenced in accordance with steps (c) and (d) of the Count. (ATX 1105 at 112-13)

Later experiments performed under similar conditions were additional, subsequent reductions to practice. (*See* FF63 (January 23, 2003 experiment); FF64 (January 28-31); FF65 (February 5); FF66 (February 6); FF67 (February 7); FF72 (February 19); FF73 (February 27); FF74 (March 7); FF75 (March 28))

JHU criticizes 454's evidence of conception and reduction to practice in a variety of ways. (*See, e.g.*, D.I. 110 at 30-31) JHU argues that the 454 experimental documents do not show a conception or reduction to practice of step (b) "based on work done with the test fragments." (*Id.* at 30) The Court disagrees. As Dr. Levy opined, the test fragments were included in microemulsions as required in step (b) of the Count. (Levy Tr. at 359:23-360:11; *see also* Sarkis Tr. at 194:11-15)

JHU contends that the "only basis that Dr. Levy and 454 provide" to show conception and reduction to practice of step (b) is that the Poisson distribution theory applies to the distribution of fragments in the microemulsion. (D.I. 110 at 30) Even if this allegation were true (it is not), JHU's own expert testified that the Poisson distribution is "always true" (Tyagi Tr. at 137:2-3, 138:25-139:1), and the Court credits Dr. Levy's testimony that the Poisson distribution would hold true with respect to 454's experiments that resulted in reductions to practice of the invention

(Levy Tr. at 359:23-360:11).

JHU argues that "the data collected (number of fragments per bead)" during the 454 experiments "is insufficient to show that the Poisson distribution was actually achieved." (D.I. 110 at 30) Again, the Court credits Dr. Levy's testimony that the Poisson distribution would hold true and predicts two or more microreactors, complying with the requirements of step (b). (Levy Tr. at 359:17-22) As explained by Dr. Levy, one could estimate the number of compartments in an emulsion by "knowing the diameter of those compartments and the volume of the aqueous solution going in." (*Id.* at 365:11-22) Based on the number of compartments, the number of fragments, and the number of beads, Dr. Levy was able to conclude that the 454 reductions to practice would have included more than one compartment with a single bead and the same fragment of DNA, "because you're able to do PCR that's detectable in the sequencing action." (*Id.* at 365:23-366:15)

The Court further credits Dr. Levy's opinion that the very fact that 454 obtained sequencing results necessarily presupposes that some nonzero number of identical test fragments were delivered to microreactors. As Dr. Levy explained, while 454's experiments were not designed to test the Poisson distribution, and therefore cannot demonstrate the percent of instances in which there is a single fragment on a single bead, the experiments do show "sequence data." (Levy Tr. at 360:9-361:3) This is itself confirmation of there being at least one instance of a single fragment on a single bead: "[I]t is very clear that you only get sequence data from the experimental setup. You only get sequence data if there is one fragment on one bead going into the amplification." (Levy Tr. at 360:20-24; *see also id.* at 496:8-12 ("You can't use this data to back-calculate the percentages, but it absolutely assuredly tells you that there were

individual beads with individual fragments that amplified and were capable of being sequenced and could be mapped to the, in this case, the identifier genome.") Dr. Tyagi ultimately agreed that if one gets a sequence (as 454 did), this means that there was only one sequence on the bead. (Tyagi Tr. at 546: 6-8 ("I would agree with Dr. Levy, that sequence, if you get a sequence, that means there was only one sequence on the bead."))

JHU argues that the fact that test fragments were added to emulsions separately from adenovirus means amplification and sequencing would have produced "exactly the same signal" whether there were 1 or 100 fragments in a microreactor. (D.I. 110 at 31; Tr. at 577:3-10) JHU's arguments on this issue are vague but appear to reflect its broader speculation that there is no way to be sure step (b) was satisfied by two or more microreactors containing ***only one*** of the same DNA fragment and a single bead. The Court credits the testimony of Dr. Sarkis, as well as the documentary evidence from Dr. Leamon's notebook, and is persuaded the record demonstrates compartments of "about the right size" for containing single bead-single fragment combinations. (Sarkis Tr. at 190:5-191:10; *see also id.* at 197:2-7) Moreover, the Court credits Dr. Sarkis's testimony that his January 14-15 experiment produced at least two microreactors complying with step (b). (*Id.* at 200:15-22)

JHU asserts (without showing) that there is no evidence that the beads to which the test fragments were allegedly attached were capable of hybridizing to the test fragments. (D.I. 110 at 31) The Court disagrees. Dr. Sarkis's lab notebook and testimony from Dr. Berka indicate that 454's standard practice was to wash and perform other actions meant to remove unbound beads, leaving only the beads and fragments bound to them (if any) for analysis. (*See generally* ATX 1105 at 112; Tr. at 306:23-313:12 (noting that, after washing and PCR cycling, ***beads*** and any

fragments bound thereto were analyzed, not unbound fragments); *see also* Sarkis Tr. at 217:1-4)

JHU further contends in its post-trial briefing (without citing to the record) that the sequencing primers used for test fragments raise questions about whether the 454 experiments practiced the Count. (D.I. 110 at 31) 454 responds that this argument was never presented at any earlier point in this case, and that there is no record evidence cited in support of it, so JHU's position in this regard is not entitled to any evidentiary weight. (D.I. 118 at 28) The Court agrees and will disregard JHU's attorney argument – which is unsupported by anything in the record.

3. 454's Conception and Reductions to Practice are Corroborated

454 has shown by a preponderance of the evidence that it conceived and reduced to practice the invention of the Count as described above and has come forward with credible, persuasive non-inventor evidence to corroborate the experiments discussed above. (*See* FF76-87) Mr. Altman corroborated production of the F6 test fragments by PCR, satisfying step (a) of the Count. (FF46) Ms. Lanza recorded the sequence of the F6 test fragment in her lab notebook, evidencing conception of step (d) and the intention of the experiments to amplify and detect F6 test fragments. (FF47) Dr. de Winter corroborated all steps of the Count with his testimony that his team performed emulsion experiments either with test fragments alone or with test fragments mixed with adenovirus. (FF53) Dr. Lanza corroborated reductions to practice in January 2003 and testified that she worked "very closely" with Dr. Sarkis at the time. (ATX 1126 ¶¶ 10-13) Mr. McDade corroborated conception as of December 20, 2002, as already discussed above, and the subsequent reductions to practice.

C. 454's Priority Claim to '071 Application

454 has proven that it is entitled to claim priority to the '071 application, because it has shown that the '071 application describes and enables a person of ordinary skill in the art to practice at least one embodiment within the scope of the Count. (FF107-28) The '071 application discloses use of restriction endonuclease digestion for the creation of template DNA used in conformance with step (a) of the Count. (FF109, 114) The '071 also discloses use of commercially available kits for DNA isolation, which would have necessarily included kits that have more than one of the same DNA fragment. (FF111) Use of restriction enzymes on DNA fragments from commercially available kits would result in practicing step (a) of the Count. (FF114-15)

The '071 application discloses step (b) of the Count. (FF117-25) The '071 application specifically states: "The average size of the emulsion capsules must be optimized to maximize the number of single beads containing single strands of DNA, that can be incorporated within a single emulsion volume." (FF117) The foregoing refers to use of the DNA template generated during step (a), as described above. (FF118) The '071 application discloses enough guidance and the necessary parameters to enable someone of ordinary skill in the art to practice the Count. (*See* FF119-25)

Finally, the '071 application discloses steps (c) and (d) of the Count, as described in the findings of fact. (FF126-27)

JHU argues that the '071 application does not disclose the full scope of the invention because it does not disclose methods involving double-stranded DNA template used in step (a) or use of non-pre-hybridized DNA separate from beads delivered to microreactors according to step

(b). (D.I. 110 at 10) JHU's contentions rely on a flawed legal premise. In order to support a claim of priority, it is not necessary for 454 to prove written description and enablement of the ***full scope*** of the Count by the '071 application. *See Hunt*, 523 F.2d at 1389. Instead, 454 need only prove written description and enablement of an embodiment – which 454 has done, as explained elsewhere in this Opinion. Nevertheless, the Court finds that the '071 application's disclosures ***do*** enable even what JHU characterizes as the "full scope" of the invention.

Regarding JHU's arguments as to step (a), the '071 application discloses use of single-stranded DNA hybridized to a bead via oligonucleotide primer such that a short region of double-stranded DNA would be created at the bond. (Levy Tr. at 404:10-22) Thus, the '071 application discloses both double- and single-stranded DNA. Moreover, Dr. Levy testified that delivery of only double-stranded DNA to an emulsion instead of single-stranded DNA would not have any effect on the outcome of the method in the Count. (*Id.* at 405:8-16) There would be no significant difference in how one would perform the method of the Count by using only double-stranded DNA in step (a). (*Id.* at 405:17-406:3)

With respect to JHU's argument that the '071 application does not describe or enable delivery of DNA separate from a bead into a microreactor, the Court is persuaded by Dr. Levy's opinion that a person of ordinary skill in the art would know how to deliver DNA separate from beads, given the disclosure of a pre-hybridized embodiment, such as the one in the '071 application. (*Id.* at 406:4-20)

JHU does not argue that the '071 application (or the '592 application) fails to describe or enable steps (c) or (d) of the Count.

D. 454's Priority Claim to '592 Application

454 has proven that it is entitled to claim priority to the '592 application, because it has shown that the '592 application describes and enables a person of ordinary skill in the art to practice at least one embodiment within the scope of the Count. (FF107-28) The '592 application discloses everything that is in the '071 application – plus additional detail. (*Compare* ATX 1013 ('592 application) *with* ATX 1015 ('071 application)) Thus, for at least the reasons given above with respect to the '071 application, the '592 application also qualifies as a constructive reduction to practice.

E. JHU's Conception and Reduction to Practice

The Court previously determined that JHU conceived of the invention on June 5, 2003 and exercised reasonable diligence until reduction to practice on July 5, 2003. (D.I. 97 at 12, 16) JHU has failed to prove that it is entitled to a priority date earlier than June 5, 2003. The only non-inventor corroborating evidence cited by JHU in support of its arguments for an earlier priority date fails to disclose the following required elements of the Count, as explained by 454 in its answering brief and in the Court's findings of fact: (1) delivering a plurality of molecules of the same fragment of DNA into microreactors; (2) any type of emulsion; (3) any microreactor; (4) having a single bead in a microreactor; and (5) having a single molecule of a DNA fragment in a microreactor. (*See* D.I. 118 at 32; *see also* FF140-62) Because JHU has cited insufficient corroboration of conception and reduction to practice, JHU has failed to carry its burden of proving, by a preponderance of the evidence, an earlier priority date. *See Marteki*, 579 F.3d at 1375.

F. Conclusion as to Priority

454 has proven (1) conception by at least December 2002; (2) actual reduction to practice by at least January 15, 2003; and (3) constructive reductions to practice of the Count by April 23, 2003, the filing date of the '071 application, and June 6, 2003, the filing date of the '592 application. As previously determined by the Court, JHU has proven a conception date of June 5, 2003 and a reduction to practice date of July 5, 2003, with diligence during the intervening time period sufficient to support a June 5, 2003 priority date. (D.I. 97 at 12, 16) Accordingly, the Court is compelled to hold that 454 prevails on the parties' priority dispute, as 454 has proven that it was the first to conceive of the invention and the first to reduce it to practice.

II. VALIDITY

A. Legal Standards

1. Written Description

Paragraph 1 of 35 U.S.C. § 112 states in pertinent part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .[13]

The statute sets out separate requirements for written description and enablement. *See Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (holding that written description and enablement requirements are separate). Yet these requirements "often rise and

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[13]The patent statute was amended in September 2011 by the America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 300-01 (2011). The pre-AIA version of § 112 applies in this case. The post-AIA version of this portion of the statute (§ 112(a)) is identical to the pre-AIA verison.

fall together." *Id.* at 1352. The parties agree that, in a case brought under § 146 arising from an interference, invalidity under § 112 must be proved by a preponderance of the evidence. (*See* Tr. at 31-32, 45) The Court agrees that a preponderance of the evidence standard applies. *See Bruning v. Hirose*, 1998 WL 690851, at *3-5 (Fed. Cir. Sept. 29, 1998).

Whether a specification satisfies the written description requirement is a question of fact. *See GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 729 (Fed. Cir. 2014); *see also Alcon, Inc. v. Teva Pharms. USA, Inc.*, 664 F. Supp. 2d 443, 468 (D. Del. 2009) ("Satisfaction of the written description requirement is a fact-based inquiry, depending on 'the nature of the claimed invention and the knowledge of one skilled in the art at the time an invention is made and a patent application is filed.'") (quoting *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008)).

To comply with the written description requirement, a patent's specification "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad*, 598 F.3d at 1351 (internal brackets and quotation marks omitted). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. . . . [T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* "[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Id.* at 1352. However, "a description that merely renders the invention obvious does not satisfy the requirement." *Id.*

2. Enablement

"Enablement is a question of law based on underlying factual findings." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). "'To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'" *Id.* (quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)) (internal quotation marks omitted). "Enablement serves the dual function in the patent system of ensuring adequate disclosure of the claimed invention and of preventing claims broader than the disclosed invention." *Id.* at 1380-81. "Thus, a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage." *Id.* at 1381. "The scope of the claims must be less than or equal to the scope of the enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Id.* (internal quotation marks omitted).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* Although "a specification need not disclose what is well known in the art," "[t]ossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech*, 108 F.3d at 1366. A patent "cannot simply rely on the knowledge of a person of ordinary skill to

serve as a substitute for the missing information in the specification." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010).

3. Anticipation

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *see also In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985) (stating patent is invalid for anticipation where "each limitation of a claim [can] be found in a single reference, practice, or device"). A "printed publication in this or a foreign country" is anticipatory prior art if it discloses the claimed subject matter "before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a).[14] "The dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim limitation was disclosed in that single reference." *Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1192 (Fed. Cir. 2003). Whether a claim is anticipated is a question of fact. *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006).

In this case, which arises from an interference, anticipation must be proved by a preponderance of the evidence. *See Bruning v. Hirose*, 161 F.3d 681, 685-86 (Fed. Cir. 1998) ("During an interference involving a patent issued from an application that was co-pending with the interfering application, the appropriate standard of proof for validity challenges is the preponderance of the evidence standard.").

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[14]The Court again refers to the pre-AIA version of the patent statute, which governs in this case.

"A showing that a patent was conceived at an earlier date [than the date of a prior art reference] and reduced to practice with reasonable diligence is called an effort to swear behind" a prior art reference. *Stamps.com Inc. v. Endicia, Inc.*, 437 F. App'x 897, 907 (Fed. Cir. 2011); *see also Moll v. Northern Telecom, Inc.*, 1995 WL 676420, at *4 n.1 (E.D. Pa. Nov. 8, 1995) ("[B]y permitting a patent applicant to 'swear behind' the prior reference under 37 C.F.R. § 1.131, a patent examiner effectively removes the prior art as a bar to patentability."). "The requirement for the corroboration of inventor testimony applies to efforts to swear behind a prior art reference." *Stamps*, 437 F. App'x at 908.

B. Whether the '240 Application Meets the Written Description and Enablement Requirements

The Court has already determined that the '071 and '592 applications disclose the full scope of the invention, for reasons explained above. Specifically, the Court concluded that the '071 application's disclosure of hybridized DNA to beads discloses both single- and double-stranded DNA and that the '071 application's disclosure of the pre-hybridized embodiment provides written description and enablement support for a non-pre-hybridized embodiment. (Levy Tr. at 404:10-22, 405:8-406:20) The '240 application incorporates the '071 and '592 applications by reference. (ATX 1001 at 3-8) Thus, the '240 application also adequately describes and enables the full scope of the invention. *See Harari v. Lee*, 656 F.3d 1331, 1338 (Fed. Cir. 2011) (holding that patent application incorporated by reference could supply written description support).

Thus, while JHU is correct that 454 must satisfy § 112's written description and enablement requirements for the full scope of the claims it seeks to retain (i.e., the claims of the

'305 patent, which is the issued patent that is the progeny of the '240 application), *see Falko-Gunter*, 448 F.3d at 1362, 454 has met this burden by the requisite preponderance of the evidence.

C. Whether '240 Application is Anticipated by the Dressman Reference

JHU argues that the '240 application is anticipated by the Dressman reference. (D.I. 110 at 1-2) The Court disagrees. The date of the Dressman reference is July 22, 2003. (*Id.*) The Court has determined, as discussed above, that 454 is entitled to claim priority to the '071 and '592 applications for written description and enablement of the full scope of the Count. The priority dates of these applications antedate the Dressman reference. Therefore, the Court agrees with 454 that the Dressman reference is not prior art to the '240 application and cannot anticipate under § 102. (*See* D.I. 118 at 7-10)[15]

D. Conclusion as to Validity

For the foregoing reasons, the Court concludes that JHU has failed to prove that the '240 application is invalid under either of §§ 112 or 102.

CONCLUSION

Plaintiffs have failed to prove by a preponderance of the evidence that they are entitled to priority. Plaintiffs have also failed to prove by a preponderance of the evidence that the '240 application is invalid.

An appropriate Order will be entered.

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[15]For this reason, JHU's reliance on *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247 (Fed. Cir. 2004), is unavailing. Moreover, *Chiron* is distinguishable, as argued by 454 (D.I. 118 at 8-9), because the separate delivery of beads and fragments of either single- or double-stranded DNA into microreactors was not unpredictable, nascent technology like the technology at issue in *Chiron*.